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(71) Applicants *(for all designated States except US)*: **RIBOZYME PHARMACEUTICALS, INCORPORATED** [US/US]; 2950 Wilderness Place, Boulder, CO 80301 (US). **CHIRON CORPORATION** [US/US]; 4560 Horton Street, Emeryville, CA 94608-2916 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ESCOBEDO, Jaime** [US/US]; 1470 Livorna Road, Alamo, CA 94507 (US). **MCSWIGGEN, James** [US/US]; 4866 Franklin Drive, Boulder, CO 80301 (US). **PAVCO, Pamela** [US/US]; 705 Barberry Circle, Lafayette, CO 80026 (US). **STINCHCOMB, Dan** [US/US]; 8409 South Country Road 3, Ft. Collins, CO 80528 (US). **SANDBERG, Jennifer** [US/US]; 620 Bluegrass Drive, Longmont, CO 80503 (US). **GORDON, Gilad** [US/US]; 3605 Silver Plume Lane, Boulder, CO 80303 (US).

(74) Agent: **TERPSTRA, Anita, J.**; McDonnell Boehnen Hulbert & Berghoff, Suite 3200, 300 South Wacker Drive, Chicago, IL 60606 (US).

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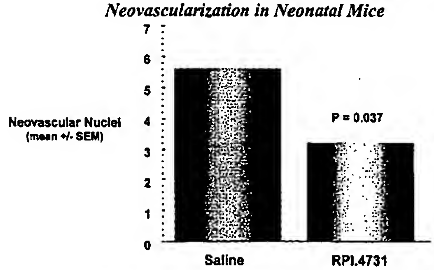
(54) Title: NUCLEIC ACID BASED MODULATION OF FEMALE REPRODUCTIVE DISEASES AND CONDITIONS

RPI.4731 Reduces Hypoxia-Induced Retinal Neovascularization in Neonatal Mice



SEQ ID NO: 5978

Results: ~40% decrease in retinal neovascularization following two intraocular injections of RPI.4731

(57) Abstract: The present invention relates to nucleic acid molecules, including dsRNA, siRNA, antisense, 2,5-A chimeras, aptamers, and enzymatic nucleic acid molecules, such as hammerhead ribozymes, DNAzymes, and allozymes, which modulate the expression of vascular endothelial growth factor receptor (VEGF) and/or vascular endothelial growth factor receptor (VEGFr) genes for the treatment and/or diagnosis of diseases and conditions associated with angiogenesis, such as cancer, tumor angiogenesis, or ocular indications such as diabetic retinopathy, or age related macular degeneration, proliferative diabetic retinopathy, hypoxia-induced angiogenesis, rheumatoid arthritis, psoriasis, wound healing, and female reproductive disorders and conditions, including but not limited to endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), and menopausal dysfunction.

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NUCLEIC ACID BASED MODULATION OF FEMALE REPRODUCTIVE DISEASES AND CONDITIONS

This patent application claims priority from Sandberg *et al.*, USSN 60/334,461, filed November 30, 2001, entitled "Method and Reagent for the Modulation of Female Reproductive Diseases and Conditions" and Pavco et al., USSN 10/138,674, filed May 3, 2002, which is a continuation in part of Pavco *et al.*, USSN 09/870,161, which is a continuation-in-part of Pavco *et al.*, USSN 09/708,690, filed November 7, 2000, which is a continuation-in-part of Pavco *et al.*, USSN 09/371,722, filed August 10, 1999, which is a continuation-in-part of Pavco *et al.*, USSN 08/584,040, filed January 11, 1996, which claims the benefit of Pavco *et al.*, USSN 60/005,974, filed on October 26, 1995; these earlier applications are entitled "Method and Reagent for Treatment of Diseases or Conditions Related to Levels of Vascular Endothelial Growth Factor Receptor". Each of these applications is hereby incorporated by reference herein in it's entirety including the drawings and tables.

Technical Field Of The Invention

This invention relates to methods and reagents for the treatment of diseases or conditions relating to the levels of expression of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor(s). Specifically, the instant invention features nucleic-acid based molecules and methods that modulate the expression of vascular endothelial growth factor and/or vascular endothelial growth factor receptors, such as VEGFR1 and/or VEGFR2, that are useful in preventing, treating, controlling and/or diagnosing disorders and conditions related to angiogenesis, including but not limited to cancer, tumor angiogenesis, or ocular indications such as diabetic retinopathy, or age related macular degeneration, proliferative diabetic retinopathy, hypoxia-induced angiogenesis, rheumatoid arthritis, psoriasis, wound healing, endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), and menopausal dysfunction.

Background Of The Invention

The following is a discussion of relevant art, none of which is admitted to be prior art to the present invention.

VEGF, also referred to as vascular permeability factor (VPF) and vasculotropin, is a potent and highly specific mitogen of vascular endothelial cells (for a review see Ferrara, 1993 *Trends Cardiovas. Med.* 3, 244; Neufeld *et al.*, 1994, *Prog. Growth Factor Res.* 5, 89). VEGF-induced neovascularization is implicated in various pathological conditions such as tumor angiogenesis, or ocular indications such as diabetic retinopathy, or age related macular degeneration, proliferative diabetic retinopathy, hypoxia-induced angiogenesis, rheumatoid arthritis, psoriasis, wound healing and others.

VEGF, an endothelial cell-specific mitogen, is a 34-45 kDa glycoprotein with a wide range of activities that include promotion of angiogenesis, enhancement of vascular-permeability and others. VEGF belongs to the platelet-derived growth factor (PDGF) family of growth factors with approximately 18% homology with the A and B chain of PDGF at the amino acid level. Additionally, VEGF contains the eight conserved cysteine residues common to all growth factors belonging to the PDGF family (Neufeld *et al., supra*). VEGF protein is believed to exist predominantly as disulfide-linked homodimers; monomers of VEGF have been shown to be inactive (Plouet *et al.*, 1989 *EMBO J.* 8, 3801).

VEGF exerts its influence on vascular endothelial cells by binding to specific high-affinity cell surface receptors. Covalent cross-linking experiments with ^{125}I-labeled VEGF protein have led to the identification of three high molecular weight complexes of 225, 195 and 175 kDa presumed to be VEGF and VEGF receptor complexes (Vaisman *et al.*, 1990 *J. Biol. Chem.* 265, 19461). Based on these studies VEGF-specific receptors of 180, 150 and 130 kDa molecular mass were predicted. In endothelial cells, receptors of 150 and 130 kDa have been identified. The VEGF receptors belong to the superfamily of receptor tyrosine kinases (RTKs) characterized by a conserved cytoplasmic catalytic kinase domain and a hydrophilic kinase sequence. The extracellular domains of the VEGF receptors consist of seven immunoglobulin-like domains that are thought to be involved in VEGF binding functions.

The two most abundant and high-affinity receptors of VEGF are flt-1 (VEGFR1) (*fms*-like tyrosine kinase) cloned by Shibuya *et al.,* 1990 *Oncogene* 5, 519 and KDR (VEGFR2) (kinase-insert-domain-containing receptor) cloned by Terman *et al.*, 1991 *Oncogene* 6, 1677. The murine homolog of KDR, cloned by Mathews *et al.*, 1991, *Proc. Natl. Acad. Sci.*, USA, 88, 9026, shares 85% amino acid homology with KDR and is termed as flk-1 (fetal liver kinase-1). The high-affinity binding of VEGF to its receptors is modulated by cell surface-associated heparin and heparin-like molecules (Gitay-Goren *et al.*, 1992 *J. Biol. Chem.* 267, 6093).

VEGF expression has been associated with several pathological states such as tumor angiogenesis, several forms of blindness, rheumatoid arthritis, psoriasis and others. In addition, a number of studies have demonstrated that VEGF is both necessary and sufficient for neovascularization. Takashita *et al.,* 1995 *J. Clin. Invest.* 93, 662, demonstrated that a single injection of VEGF augmented collateral vessel development in a rabbit model of ischemia. VEGF also can induce neovascularization when injected into the cornea. Expression of the VEGF gene in CHO cells is sufficient to confer tumorigenic potential to the cells. Kim *et al., supra* and Millauer *et al., supra* used monoclonal antibodies against VEGF or a dominant negative form of VEGFR2 receptor to inhibit tumor-induced neovascularization.

During development, VEGF and its receptors are associated with regions of new vascular growth (Millauer et al., 1993 Cell 72, 835; Shalaby et al., 1993 J. Clin. Invest. 91, 2235). Furthermore, transgenic mice lacking either of the VEGF receptors are defective in blood vessel formation and these mice do not survive; VEGFR2 appears to be required for differentiation of endothelial cells, while VEGFR1 appears to be required at later stages of vessel formation (Shalaby et al., 1995 Nature 376, 62; Fung et al., 1995 Nature 376, 66). Thus, these receptors apparently need to be present to properly signal endothelial cells or their precursors to respond to vascularization-promoting stimuli.

Increasing evidence suggests that the VEGF family may also be involved with both the etiology and maintenance of peritoneal endometriosis. Peritoneal endometriosis is a significant debilitating gynecological problem of widespread prevalence. It is now generally accepted that the pathogenesis of peritoneal endometriosis involves the implantation of exfoliated endometrium. Maintenance of exfoliated endometrial tissue is dependent upon the generation and maintenance of an extensive blood supply both within and surrounding the ectopic tissue.

Endometriosis is a disease affecting an estimated 77 million women and teenagers worldwide. Endometriosis is a leading cause of infertility, chronic pelvic pain and hysterectomy. Endometriosis can be characterized when endometrial tissue (the tissue inside the uterus which builds up and is shed each month during menses) is found outside the uterus, in other areas of the body. The endometrial tissue can respond to hormonal commands each month and break down and bleed. However, unlike the endometrium, these tissue deposits have no way of leaving the body. The result is internal bleeding, degeneration of blood and tissue shed from the growths, inflammation of the surrounding areas, expression of irritating enzymes and formation of scar tissue. In addition, depending on the location of the growths,

interference with the bowel, bladder, intestines and other areas of the pelvic cavity can occur. Endometrial tissue has even been found lodged in the skin and at other extrapelvic locations like the arm, leg and even brain.

Currently, the presence of Endometriosis can only be confirmed through surgery such as laparoscopy, but can be suspected based on symptoms, physical findings and diagnostic tests. Endometriosis can be treated in many different ways, both surgically and medically. Most commonly, surgery will be performed during which the disease will be excised, ablated, fulgarated, cauterized or otherwise removed, and adhesions will also be freed. Surgeries include but are not limited to laparoscopy; laparotomy; presacral and uterosacral and various levels of hysterectomies, where some or all of the reproductive organs are removed. Often, this method will only relieve the symptoms associated with growths on the reproductive organs, not the bowels or kidneys and related areas where Endometriosis can be present.

There are several drugs used to treat Endometriosis that are utilized either alone or in combination with surgery. These include contraceptives, GnRH agonists, and/or synthetic hormones. GnRH agonists are commonly used on women in all stages of the disease and may sometimes have serious side affects. GnRH (gonadotropin releasing hormone) analogues are classified into 2 groups: agonists and antagonists. Agonists are commonly used in the treatment of Endometriosis by suppressing the manufacture of follicle stimulating hormone (FSH) and luteinizing hormone (LH), common hormones required in ovulation. When they are not secreted, the body will go into "pseudo-menopause," stalling the growth of more implants. However, these are again only stop-gap measures that can be utilized only for short term intervals. Once the body returns to it's normal state, the Endometriosis will again begin to implant itself.

Angiogenesis is likely to be involved in the pathogenesis of endometriosis. According to the transplantation theory, when the exfoliated endometrium is attached to the peritoneal layer, the establishment of a new blood supply is essential for the survival of the endometrial implant and development of endometriosis (Donnez *et al.*, 1998, *Hum. Reprod.*, 13, 1686-1690). Endometrial growth and repair after menstruation are associated with profound angiogenesis. Abnormalities in these processes result in excessive or unpredictable bleeding patterns and are common in many women. It is therefore important to understand which factors regulate normal endometrial angiogenesis. Vascular endothelial growth factor (VEGF) is an endothelial cell-specific mitogen that plays an important role in normal and pathological angiogenesis (Fasciani *et al.*, 2000, *Mol. Hum. Reprod.*, 6, 50-54; Sharkey *et al.*, 2000, *J. Clin. Endocrinol. Metab.*, 85, 402-409). Sources of this factor include the eutopic

endometrium, ectopic endometriotic tissue and peritoneal fluid macrophages. Important to its etiology is the correct peritoneal environment in which the exfoliated endometrium is seeded and implants. Established ectopic tissue is then dependent on the peritoneal environment for its survival, an environment that supports angiogenesis. The increasing knowledge of the involvement of the VEGF family in endometriotic angiogenesis raises the possibility of novel approaches to its medical management, with particular focus on the anti-angiogenic control of the action of VEGF (McLaren, 2001, *Hum. Reprod. Update,* 6, 45-55).

Pavco *et al.*, International PCT Publication No. WO 97/15662, describes methods and reagents for treating diseases or conditions related to levels of vascular endothelial growth factor receptor.

Robinson, International PCT Publication No. WO 95/04142, describes the use of certain antisense oligonucleotides targeted against VEGF RNA to inhibit VEGF expression.

Jellinek *et al.*, 1994 *Biochemistry* 33, 10450 describe the use of specific VEGF-specific high-affinity RNA aptamers to inhibit the binding of VEGF to its receptors.

Rockwell and Goldstein, International PCT Publication No. WO 95/21868, describe the use of certain anti-VEGF receptor monoclonal antibodies to neutralize the effect of VEGF on endothelial cells.

Pappa, International PCT Publication No. WO 01/32920, describes inhibitors, including certain ribozyme and antisense nucleic acid molecules, of specific genes, including cathepsin D, AEBP-1, stromelysin-3, cystatin B, protease inhibitor 1, sFRP4, gelsolin, IGFBP-3, dual specificity phosphatase 1, PAEP, Ig gamma chain, ferritin, complement component 3, pro-alpha-1 type III collagen, proline 4-hydroxylase, alpha-2 type I collagen, claudin-4, melanoma adhesion protein, procollagen C-endopeptidase enhancer, nascent-polypeptide-associated complex alpha polypeptide, elongation factor 1 alpha (EF-1-alpha), vitamin D3 25 hydroxylase, CSRP-1, steroidogenic acute regulatory protein, apolipoprotein E, transcobalamin II, prosaposin, early growth response 1 (EGR1), ribosomal protein S6, adenosine deaminase RNA-specific protein, RAD21, guanine nucleotide binding protein beta polypeptide 2-like 1 (RACK1) and podocalyxin genes which are all differentially expressed in tissues within individual patients with endometriosis.

Labarbera *et al.*, International PCT Publication No. WO 00/73416, describes specific antisense nucleic acid molecules targeting follicle-stimulating hormone receptor.

Storella *et al.*, International PCT Publication No. WO 99/63116, describes modulators of Prothymosin gene products for treating endometriosis, including certain ribozymes and antisense nucleic acid molecules.

Summary Of The Invention

This invention features nucleic acid-based molecules, for example, enzymatic nucleic acid molecules, allozymes, antisense nucleic acids, 2-5A antisense chimeras, triplex forming oligonucleotides, decoy RNA, dsRNA, siRNA, aptamers, and antisense nucleic acids containing nucleic acid cleaving chemical groups, and methods to modulate vascular endothelial growth factor (VEGF) and/or vascular endothelial growth factor receptor (VEGFr) gene expression. Non-limiting examples of genes that encode vascular endothelial growth factor receptors of the invention include VEGFR1, VEGFR2 or combinations thereof. In particular, the instant invention features nucleic acid-based molecules and methods that modulate the expression of vascular endothelial growth factor and/or vascular endothelial growth factor receptors, such as VEGFR1 and/or VEGFR2, that are useful in preventing, treating, controlling, and/or diagnosing angiogenesis related diseases and conditions, including but not limited to tumor angiogenesis, cancers such as breast cancer, lung cancer, colorectal cancer, renal cancer, pancreatic cancer, or melanoma, or ocular indications such as diabetic retinopathy, or age related macular degeneration, and female reproductive disorders and conditions, including but not limited to endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), and menopausal dysfunction.

In one embodiment, the invention features one or more nucleic acid-based molecules and methods that independently or in combination modulate the expression of gene(s) encoding vascular endothelial growth factor receptors. Specifically, the present invention features nucleic acid molecules that modulate the expression of VEGF (for example Genbank Accession No. NM_003376), VEGFR1 receptor (for example Genbank Accession No. NM_002019), and VEGFR2 receptor (for example Genbank Accession No. NM_002253) that are useful in preventing, treating, controlling, and/or diagnosing tumor angiogenesis, cancers such as breast cancer, lung cancer, colorectal cancer, renal cancer, pancreatic cancer, or melanoma, or ocular indications such as diabetic retinopathy, or age related macular degeneration, and female reproductive disorders and conditions, including but not limited to

endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), and menopausal dysfunction.

In one embodiment, the present invention features a compound having Formula I: (SEQ ID NO: 5977)

5' $g_sa_sg_su_s$ugc$\underline{\text{U}}$GAuGagg ccgaaa ggccGaaAgucugB 3'

wherein each a is 2'-O-methyl adenosine nucleotide, each g is a 2'-O-methyl guanosine nucleotide, each c is a 2'-O-methyl cytidine nucleotide, each u is a 2'-O-methyl uridine nucleotide, each A is adenosine, each G is guanosine, each s individually represents a phosphorothioate internucleotide linkage, U is 2'-deoxy-2'-C-allyl uridine, and B is an inverted deoxyabasic moiety. This compound is also referred to as ANGIOZYME™ ribozyme.

In another embodiment, the present invention features a compound having **Formula II:** (SEQ ID NO: 5978).

5'-$u_sa_sc_s$ $a_s$au ucU GAu Gag gcg aaa gcc Gaa Aag aca aB-3'

wherein each **a** is 2'-O-methyl adenosine nucleotide, each **g** is a 2'-O-methyl guanosine nucleotide, each **c** is a 2'-O-methyl cytidine nucleotide, each **u** is a 2'-O-methyl uridine nucleotide, each **A** is adenosine, each **G** is guanosine, each **s** individually represents a phosphorothioate internucleotide linkage, $\underline{\text{U}}$ is 2'-deoxy-2'-C-allyl uridine, and **B** is an inverted deoxyabasic moiety.

In one embodiment, the invention features a composition comprising a nucleic acid molecule of the invention in a pharmaceutically acceptable carrier. In another embodiment, the invention features a composition comprising a compound of Formula I and/or Formula II in a pharmaceutically acceptable carrier or diluent.

In one embodiment, the invention features a method of administering to a cell, for example a mammalian cell, including a human cell, a nucleic acid molecule of the invention comprising contacting the cell with the nucleic acid molecule under conditions suitable for administration, for example in the presence of a delivery reagent such as a lipid, cationic lipid, phospholipid, or liposome. In another embodiment, the invention features a method of administering to a cell, for example a mammalian cell , including a human cell, a compound of Formula I and/or Formula IIcomprising contacting the cell with the compound under

conditions suitable for administration, for example in the presence of a delivery reagent such as a lipid, cationic lipid, phospholipid, or liposome.

In one embodiment, the present invention features a mammalian cell comprising a nucleic acid molecule of the invention, wherein the mammalian cell is, for example, a human cell. In another embodiment, the present invention also features a mammalian cell comprising the compound of Formula I and/or Formula II, wherein the mammalian cell is, for example, a human cell.

In one embodiment, the invention features a method of inhibiting angiogenesis, for example tumor angiogenesis, or ocular indications such as diabetic retinopathy, or age related macular degeneration, or endometrial neovascularization, in a subject comprising contacting the subject with a nucleic acid molecule of the invention, under conditions suitable for the inhibition. In another embodiment, the invention features a method of inhibiting angiogenesis, for example tumor angiogenesis, or ocular indications such as diabetic retinopathy, or age related macular degeneration, or endometrial neovascularization, in a subject, comprising contacting the subject with a compound of Formula I and/or Formula II, under conditions suitable for the inhibition.

In another embodiment, the invention features a method of treatment of a subjecthaving an ocular condition associated with the increased level of a VEGF receptor, for example diabetic retinopathy, or age related macular degeneration, comprising contacting cells of the subjectwith a nucleic acid molecule, such as an enzymatic nucleic acid molecule targeted against a VEGF receptor RNA, e.g., molecule according to Formula I and/or II, under conditions suitable for the treatment.

In another embodiment, the invention features a method of treatment of a subjecthaving a condition associated with an increased level of VEGR and/or a VEGF receptor, for example tumor angiogenesis, cancers such as breast cancer, lung cancer, colorectal cancer, renal cancer, pancreatic cancer, or melanoma, ocular diseases or ocular indications such as diabetic retinopathy, or age related macular degeneration, rhuematoid arthritis, psoriasis endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), or menopausal dysfunction, comprising contacting cells of the subject with a nucleic acid molecule of the invention, such as a compound of Formula I and/or Formula II, under conditions suitable for the treatment.

In yet another embodiment, the inventive method of treatment further comprises the use of one or more drug therapies under conditions suitable for the treatment. Non-limiting

examples of other drug therapies that can be used in combination with nucleic acid molecules of the invention include to 5-fluoro uridine, Leucovorin, Irinotecan (CAMPTOSAR® or CPT-11 or Camptothecin-11 or Campto), Paclitaxel, or Carboplatin, GnRH (gonadotropin releasing hormone) agonists, Lupron Depot (Leuprolide Acetate), Synarel (naferalin acetate), Zolodex (goserelin acetate), Suprefact (buserelin acetate), Danazol, or oral contraceptives including but not limited to Depo-Provera or Provera (medroxyprogesterone acetate), or any other estrogen/progesterone contraceptive.

In one embodiment, the invention features a method of administering to a mammal, for example a human, a nucleic acid molecule of the invention comprising contacting the mammal with the nucleic acid molecule under conditions suitable for the administration, for example, in the presence of a delivery reagent such as a lipid, cationic lipid, phospholipid, or liposome. In another embodiment, the invention features a method of administering to a mammal, for example a human, a compound of Formula I and/or Formula II comprising contacting the mammal with the compound under conditions suitable for the administration, for example, in the presence of a delivery reagent such as a lipid, cationic lipid, phospholipid, or liposome.

In one embodiment, the invention features a nucleic acid molecule which down regulates expression of a vascular endothelial growth factor (VEGF) and/or vascular endothelial growth factor receptor (VEGFr) gene, for example, wherein the VEGFr gene comprises VEGFR1 or VEGFR2 and any combination thereof.

In one embodiment, a nucleic acid molecule of the invention, such as an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing nucleic acid cleaving chemical groups, is adapted to treat, control and/or diagnose tumor angiogenesis, cancers such as breast cancer, lung cancer, colorectal cancer, renal cancer, pancreatic cancer, or melanoma, ocular diseases or ocular indications, such as diabetic retinopathy, or age related macular degeneration, rhuematoid arthritis, psoriasis endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), or menopausal dysfunction.

Such nucleic acid molecules are also useful for the prevention of the diseases and conditions including diabetic retinopathy, macular degeneration, neovascular glaucoma, myopic degeneration, verruca vulgaris, angiofibroma of tuberous sclerosis, port-wine stains, Sturge Weber syndrome, Kippel-Trenaumay-Weber syndrome, Osler-Weber-Rendu syndrome

and other diseases or conditions that are related to the levels of VEGFR1 or VEGFR2 in a cell or tissue.

In another embodiment, the invention features a composition in a pharmaceutically acceptable carrier or diluent, comprising the nucleic acid molecule of the instant invention.

In another embodiment, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing nucleic acid cleaving chemical groups of the invention is adapted for birth control.

In one embodiment, an enzymatic nucleic acid molecule of the invention is in a hammerhead, Inozyme, Zinzyme, DNAzyme, Amberzyme, or G-cleaver configuration.

In one embodiment, an enzymatic nucleic acid molecule of the invention comprises between 8 and 100 bases complementary to RNA of VEGFR1 and/or VEGFR2 gene. In another embodiment, an enzymatic nucleic acid molecule of the invention comprises between 14 and 24 bases complementary to RNA of VEGFR1 and/or VEGFR2 gene.

In one embodiment, a siRNA molecule of the invention comprises a double stranded RNA wherein one strand of the RNA is complementary to RNA of a VEGFR1 and/or VEGFR2 gene. In another embodiment, a siRNA molecule of the invention comprises a double stranded RNA wherein one strand of the RNA comprises a portion of a sequence of RNA having a VEGFR1 and/or VEGFR2 sequence. In yet another embodiment, a siRNA molecule of the invention comprises a double stranded RNA wherein both strands of RNA are connected by a non-nucleotide linker. Alternately, a siRNA molecule of the invention comprises a double stranded RNA wherein both strands of RNA are connected by a nucleotide linker, such as a loop or stem loop structure.

In one embodiment, a single strand component of a siRNA molecule of the invention is from about 14 to about 50 nucleotides in length. In another embodiment, a single strand component of a siRNA molecule of the invention is about 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 nucleotides in length. In yet another embodiment, a single strand component of a siRNA molecule of the invention is about 23 nucleotides in length. In one embodiment, a siRNA molecule of the invention is from about 28 to about 56 nucleotides in length. In another embodiment, a siRNA molecule of the invention is about 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52 nucleotides in length. In yet another embodiment, a siRNA molecule of the invention is about 46 nucleotides in length.

In one embodiment, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing nucleic acid cleaving chemical groups of the invention is chemically synthesized.

In another embodiment, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing nucleic acid cleaving chemical groups of the invention comprises at least one 2'-sugar modification.

In another embodiment, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acids containing nucleic acid cleaving chemical groups of the invention comprises at least one nucleic acid base modification.

In another embodiment, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing nucleic acid cleaving chemical groups of the invention comprises at least one phosphate backbone modification.

In one embodiment, the invention features a mammalian cell, for example a human cell, comprising a nucleic acid molecule of the invention.

In another embodiment, the invention features a method of reducing VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 expression or activity in a cell comprising contacting the cell with a nucleic acid molecule of the invention that modulates the expression and/or activity of VEGF and/or VEGFr, under conditions suitable for the reduction.

In another embodiment, a method of treatment of a subject having a condition associated with the level of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 is featured, wherein the method further comprises the use of one or more drug therapies under conditions suitable for the treatment.

In one embodiment, the invention features a method for treatment of a subject having tumor angiogenesis, tumor angiogenesis, cancers including but not limited to tumor and cancer types shown under Diagnosis in **Table III**, ocular diseases or ocular indications such as diabetic retinopathy, or age related macular degeneration, rhuematoid arthritis, psoriasis and/or endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular

menstrual cycles, ovulation, premenstrual syndrome (PMS), or menopausal dysfunction, comprising administering to the subject a nucleic acid molecule of the invention that modulates the expression and/or activity of VEGF and/or VEGFr under conditions suitable for the treatment.

In another embodiment, the invention features a method for birth control in a subject comprising administering to the subject a nucleic acid molecule of the invention that modulates the expression and/or activity of VEGF and/or VEGFr under conditions suitable for the treatment.

In another embodiment, the invention features a method of cleaving RNA encoded by a VEGF, VEGFR1 and/or VEGFR2 gene comprising contacting an enzymatic nucleic acid molecule of the invention having endonuclease activity with RNA encoded by a VEGFR1 and/or VEGFR2 gene under conditions suitable for the cleavage, for example, wherein the cleavage is carried out in the presence of a divalent cation, such as Mg^{2+}.

In one embodiment, a nucleic acid molecule of the invention comprises a cap structure, for example a 3',3'-linked or 5',5'-linked deoxyabasic ribose derivative, wherein the cap structure is at the 5'-end, or 3'-end, or both the 5'-end and the 3'-end of the enzymatic nucleic acid molecule.

In another embodiment, a nucleic acid molecule of the invention comprises a cap structure, for example a 3',3'-linked or 5',5'-linked deoxyabasic ribose derivative, wherein the cap structure is at the 5'-end, or 3'-end, or both the 5'-end and the 3'-end of the antisense nucleic acid molecule.

In one embodiment, the invention features an expression vector comprising a nucleic acid sequence encoding at least one nucleic acid molecule of the invention such that the vector allows expression of the nucleic acid molecule.

In another embodiment, the invention features a mammalian cell, for example, a human cellcomprising an expression vector of the invention.

In yet another embodiment, an expression vector of the invention further comprises a sequence for a nucleic acid molecule complementary to RNA encoded by a VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 gene.

In one embodiment, an expression vector of the invention comprises a nucleic acid sequence encoding two or more nucleic acid molecules of the invention, which can be the same or different.

In another embodiment, the invention features a method for treatment or control of tumor angiogenesis, cancers such as breast cancer, lung cancer, colorectal cancer, renal cancer, pancreatic cancer, or melanoma, or ocular indications such as diabetic retinopathy, or age related macular degeneration, and/or endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), or menopausal dysfunction, comprising administering to a subject a nucleic acid molecule of the invention that modulates the expression and/or activity of VEGF and/or VEGFr, such as an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing nucleic acid cleaving chemical groups of the invention, under conditions suitable for the treatment, including administering to the subject one or more other therapies, for example, 5-fluoro uridine, Leucovorin, Irinotecan (CAMPTOSAR® or CPT-11 or Camptothecin-11 or Campto), Paclitaxel, or Carboplatin.GnRH (gonadotropin releasing hormone) agonists, Lupron Depot (Leuprolide Acetate), Synarel (naferalin acetate), Zolodex (goserelin acetate), Suprefact (buserelin acetate), Danazol, or oral contraceptives including but not limited to Depo-Provera or Provera (medroxyprogesterone acetate), or any other estrogen/progesterone contraceptive.

In one embodiment, the method of treatment features a nucleic acid molecule of the invention, such as an enzymatic nucleic acid or antisense nucleic acid molecule, that comprises at least five ribose residues, at least ten 2'-*O*-methyl modifications, and a 3'- end modification, such as a 3'-3' inverted abasic moiety. In another embodiment, a nucleic acid molecule of the invention further comprises phosphorothioate linkages on at least three of the 5' terminal nucleotides.

In another embodiment, the invention features a method of administering to a mammal, for example a human, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing nucleic acid cleaving chemical groups of the invention, comprising contacting the mammal with the nucleic acid molecule under conditions suitable for the administration, for example, in the presence of a delivery reagent such as a lipid, cationic lipid, phospholipid, or liposome.

In yet another embodiment, the invention features a method of administering to a mammal an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing nucleic acid cleaving chemical groups of the invention in conjunction with other therapies, comprising contacting the mammal, for example a human, with the nucleic acid molecule and the other therapy under conditions suitable for the administration.

In another embodiment, other therapies contemplated by the instant invention that can be used in conjunction with the nucleic acid molecules of the instant invention include, but are not limited to, 5-fluoro uridine, Leucovorin, Irinotecan (CAMPTOSAR® or CPT-11 or Camptothecin-11 or Campto), Paclitaxel, or Carboplatin, GnRH (gonadotropin releasing hormone) agonists, Lupron Depot (Leuprolide Acetate), Synarel (naferalin acetate), Zolodex (goserelin acetate), Suprefact (buserelin acetate), Danazol, or oral contraceptives including but not limited to Depo-Provera or Provera (medroxyprogesterone acetate), or other estrogen/progesterone contraceptive.

In one embodiment, the invention features the use of an enzymatic nucleic acid molecule, to down-regulate the expression of VEGFR1 and/or VEGFR2 genes in the treatment or control of tumor angiogenesis, cancers such as breast cancer, lung cancer, colorectal cancer, renal cancer, pancreatic cancer, or melanoma, or ocular indications such as diabetic retinopathy, or age related macular degeneration, and/or endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), or menopausal dysfunction. Such enzymatic nucleic acid molecule can be in the hammerhead, NCH, G-cleaver, Amberzyme, Zinzyme, and/or DNAzyme motif.

In another embodiment, the invention features the use of an enzymatic nucleic acid moleculeto down-regulate the expression of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 genes, as a method of birth control. Such enzymatic nucleic acid molecule can be in the hammerhead, NCH, G-cleaver, Amberzyme, Zinzyme, and/or DNAzyme motif. In one embodiment, the nucleic acid molecules of the invention have complementarity to the substrate.sequences in **Tables V and VI**. Examples of enzymatic nucleic acid molecules of the invention are shown in **Tables V and VI**. Examples of such enzymatic nucleic acid molecules consist essentially of sequences defined in these Tables.

By "inhibit", "down-regulate", or "reduce", it is meant that the expression of the gene, or level of nucleic acids or equivalent nucleic acids encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, such as VEGFR1, VEGFR2

and/or flk-1, is reduced below that observed in the absence of the nucleic acid molecules of the invention. In one embodiment, inhibition, down-regulation or reduction with enzymatic nucleic acid molecule preferably is below that level observed in the presence of an enzymatically inactive or attenuated molecule that is able to bind to the same site on the target nucleic acid, but is unable to cleave that nucleic acid. In another embodiment, inhibition, down-regulation, or reduction with antisense oligonucleotides is preferably below that level observed in the presence of, for example, an oligonucleotide with scrambled sequence or with mismatches. In another embodiment, inhibition, down-regulation, or reduction of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 with the nucleic acid molecule of the instant invention is greater in the presence of the nucleic acid molecule than in its absence.

By "up-regulate" is meant that the expression of a gene, or level of nucleic acids or equivalent nucleic acids encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, such as VEGFR1 and/or VEGFR2, is greater than that observed in the absence of the nucleic acid molecules of the invention. For example, the expression of a gene, such as VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 gene, can be increased in order to treat, prevent, ameliorate, or modulate a pathological condition caused or exacerbated by an absence or low level of gene expression.

By "modulate" is meant that the expression of a gene, or level of nucleic acids or equivalent nucleic acids encoding one or more proteins or protein subunits, or activity of one or more proteins protein subunit(s) is up-regulated or down-regulated, such that the expression, level, or activity is greater than or less than that observed in the absence of the nucleic acid molecules of the invention.

By "enzymatic nucleic acid molecule" it is meant a nucleic acid molecule which has complementarity in a substrate binding region to a specified gene target, and also has an enzymatic activity which is active to specifically cleave a target nucleic acid. That is, the enzymatic nucleic acid molecule is able to intermolecularly cleave a nucleic acid and thereby inactivate a target nucleic acid molecule. These complementary regions allow sufficient hybridization of the enzymatic nucleic acid molecule to the target nucleic acid and thus permit cleavage. One hundred percent complementarity is preferred, but complementarity as low as 50-75% can also be useful in this invention (see for example Werner and Uhlenbeck, 1995, *Nucleic Acids Research*, 23, 2092-2096; Hammann *et al.*, 1999, *Antisense and Nucleic Acid Drug Dev.*, 9, 25-31). The nucleic acids can be modified at the base, sugar, and/or phosphate groups. The term enzymatic nucleic acid is used interchangeably with phrases such

as ribozymes, catalytic RNA, enzymatic RNA, catalytic DNA, aptazyme or aptamer-binding ribozyme, regulatable ribozyme, catalytic oligonucleotides, nucleozyme, DNAzyme, RNA enzyme, endoribonuclease, endonuclease, minizyme, leadzyme, oligozyme or DNA enzyme. All of these terminologies describe nucleic acid molecules with enzymatic activity. The specific enzymatic nucleic acid molecules described in the instant application are not limiting in the invention and those skilled in the art will recognize that all that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target nucleic acid regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart a nucleic acid cleaving and/or ligation activity to the molecule (Cech *et al.,* U.S. Patent No. 4,987,071; Cech *et al.*, 1988, 260 *JAMA* 3030).

Several varieties of naturally-occurring enzymatic nucleic acids are known presently. Each can catalyze the hydrolysis of nucleic acid phosphodiester bonds in *trans* (and thus can cleave other nucleic acid molecules) under physiological conditions. **Table I** summarizes some of the characteristics of these ribozymes. In general, enzymatic nucleic acids act by first binding to a target nucleic acid. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target nucleic acid. Thus, the enzymatic nucleic acid first recognizes and then binds a target nucleic acid through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target nucleic acid. Strategic cleavage of such a target nucleic acid will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its nucleic acid target, it is released from that nucleic acid to search for another target and can repeatedly bind and cleave new targets. Thus, a single ribozyme molecule is able to cleave many molecules of target nucleic acid. In addition, the ribozyme is a highly specific inhibitor of gene expression, with the specificity of inhibition depending not only on the base-pairing mechanism of binding to the target nucleic acid, but also on the mechanism of target nucleic acid cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme.

In one embodiment of the inventions described herein, an enzymatic nucleic acid molecule of the invention is formed in a hammerhead or hairpin motif, but can also be formed in the motif of a hepatitis delta virus, group I intron, group II intron or RNase P RNA (in association with an RNA guide sequence), *Neurospora* VS RNA, DNAzymes, NCH cleaving motifs, or G-cleavers. Examples of such hammerhead motifs are described by Dreyfus, *supra,* Rossi *et al.,* 1992, *AIDS Research and Human Retroviruses* 8, 183; of hairpin motifs

by Hampel *et al.*, EP0360257, Hampel and Tritz, 1989 *Biochemistry* 28, 4929, Feldstein *et al.*, 1989, *Gene* 82, 53, Haseloff and Gerlach, 1989, *Gene*, 82, 43, and Hampel *et al.*, 1990 *Nucleic Acids Res.* 18, 299; Chowrira & McSwiggen, US. Patent No. 5,631,359; an examples of a hepatitis delta virus motif is described by Perrotta and Been, 1992 *Biochemistry* 31, 16; examples of RNase P motifs are described by Guerrier-Takada *et al.*, 1983 *Cell* 35, 849; Forster and Altman, 1990, *Science* 249, 783; Li and Altman, 1996, *Nucleic Acids Res.* 24, 835; examples of *Neurospora* VS RNA ribozyme motifs are described by Collins (Saville and Collins, 1990 *Cell* 61, 685-696; Saville and Collins, 1991 *Proc. Natl. Acad. Sci. USA* 88, 8826-8830; Collins and Olive, 1993 *Biochemistry* 32, 2795-2799; Guo and Collins, 1995, *EMBO. J.* 14, 363); examples of Group II introns are described by Griffin *et al.*, 1995, *Chem. Biol.* 2, 761; Michels and Pyle, 1995, *Biochemistry* 34, 2965; Pyle *et al.*, International PCT Publication No. *WO 96/22689*; an example of a Group I intron is described by Cech *et al.*, U.S. Patent 4,987,071; and examples of DNAzymes are described by Usman *et al.*, International PCT Publication No. WO 95/11304; Chartrand *et al.*, 1995, *NAR* 23, 4092; Breaker *et al.*, 1995, *Chem. Bio.* 2, 655; Santoro *et al.*, 1997, *PNAS* 94, 4262, and Beigelman *et al.*, International PCT publication No. WO 99/55857. NCH cleaving motifs are described in Ludwig & Sproat, International PCT Publication No. WO 98/58058; and G-cleavers are described in Kore *et al.*, 1998, *Nucleic Acids Research* 26, 4116-4120 and Eckstein *et al.*, International PCT Publication No. WO 99/16871. Additional motifs such as the Aptazyme (Breaker *et al.*, WO 98/43993), Amberzyme (Beigelman *et al.*, U.S. Serial No. 09/301,511) and Zinzyme (**Figure 7**) (Beigelman *et al.*, U.S. Serial No. 09/918,728), all included by reference herein including drawings, can also be used in the present invention. These specific motifs or configurations are not limiting in the invention and those skilled in the art will recognize that all that is important in an enzymatic nucleic acid molecule of this invention is that it have a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart a RNA cleaving activity to the molecule (Cech *et al.*, U.S. Patent No. 4,987,071).

By "nucleic acid molecule" as used herein is meant a molecule having nucleotides. The nucleic acid can be single, double, or multiple stranded and can comprise modified or unmodified nucleotides or non-nucleotides or various mixtures and combinations thereof.

By "enzymatic portion" or "catalytic domain" is meant that portion/region of a enzymatic nucleic acid molecule essential for cleavage of a nucleic acid substrate (for example see **Figure 6**).

By "substrate binding arm" or "substrate binding domain" is meant that portion/region of a enzymatic nucleic acid which is able to interact, for example via complementarity (*i.e.*, able to base-pair with), with a portion of its substrate. Preferably, such complementarity is 100%, but can be less if desired. For example, as few as 10 bases out of 14 can be base-paired (see for example Werner and Uhlenbeck, 1995, *Nucleic Acids Research*, 23, 2092-2096; Hammann *et al.*, 1999, *Antisense and Nucleic Acid Drug Dev.*, 9, 25-31). Examples of such arms are shown generally in **Figures 6-8**. That is, these arms contain sequences within a enzymatic nucleic acid which are intended to bring enzymatic nucleic acid and target nucleic acid together through complementary base-pairing interactions. An enzymatic nucleic acid of the invention can have binding arms that are contiguous or non-contiguous and can be of varying lengths. The length of the binding arm(s) are preferably greater than or equal to four nucleotides and of sufficient length to stably interact with the target nucleic acid; preferably 12-100 nucleotides; more preferably 14-24 nucleotides long (see for example Werner and Uhlenbeck, *supra;* Hamman *et al., supra;* Hampel *et al.*, EP0360257; Berzal-Herranz *et al.*, 1993, *EMBO J.*, 12, 2567-73) or between 8 and 14 nucleotides long. If two binding arms are chosen, the design is such that the length of the binding arms are symmetrical (*i.e.*, each of the binding arms is of the same length; *e.g.*, four and four, five and five nucleotides, or six and six nucleotides, or seven and seven nucleotides long) or asymmetrical (*i.e.*, the binding arms are of different length; *e.g.*, three and five, six and three nucleotides; three and six nucleotides long; four and five nucleotides long; four and six nucleotides long; four and seven nucleotides long; and the like).

By "Inozyme" or "NCH" motif or configuration is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described as NCH Rz in **Figure 6** and in Ludwig *et al.*, International PCT Publication No. WO 98/58058 and US Patent Application Serial No. 08/878,640. Inozymes possess endonuclease activity to cleave nucleic acid substrates having a cleavage triplet NCH/, where N is a nucleotide, C is cytidine and H is adenosine, uridine or cytidine, and "/" represents the cleavage site. H is used interchangeably with X. Inozymes can also possess endonuclease activity to cleave nucleic acid substrates having a cleavage triplet NCN/, where N is a nucleotide, C is cytidine, and "/" represents the cleavage site. "I" in **Figure 6** represents an Inosine nucleotide, preferably a ribo-Inosine or xylo-Inosine nucleoside.

By "G-cleaver" motif or configuration is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described as G-cleaver Rz in **Figure 6** and in Eckstein *et al.*, US 6,127,173. G-cleavers possess endonuclease activity to cleave nucleic acid substrates having a cleavage triplet NYN/, where N is a nucleotide, Y is uridine or cytidine and "/"

represents the cleavage site. G-cleavers can be chemically modified as is generally shown in **Figure 6.**

By "amberzyme" motif or configuration is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described in Beigelman *et al.*, International PCT publication No. WO 99/55857 and US Patent Application Serial No. 09/476,387. Amberzymes possess endonuclease activity to cleave nucleic acid substrates having a cleavage triplet NG/N, where N is a nucleotide, G is guanosine, and "/" represents the cleavage site. Amberzymes can be chemically modified to increase nuclease stability through substitutions using modified nucleotides. In addition, differing nucleoside and/or non-nucleoside linkers can be used to substitute the 5'-gaaa-3' loops shown in the figure. Amberzymes represent a non-limiting example of an enzymatic nucleic acid molecule that does not require a ribonucleotide (2'-OH) group within its own nucleic acid sequence for activity.

By "zinzyme" motif or configuration is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described in **Figure 7** and in Beigelman *et al.*, International PCT publication No. WO 99/55857 and US Patent Application Serial No. 09/918,728. Zinzymes possess endonuclease activity to cleave nucleic acid substrates having a cleavage triplet including but not limited to YG/Y, where Y is uridine or cytidine, and G is guanosine and "/" represents the cleavage site. Zinzymes can be chemically modified to increase nuclease stability through substitutions as are generally shown in **Figure 7**, including substituting 2'-O-methyl guanosine nucleotides for guanosine nucleotides. In addition, differing nucleotide and/or non-nucleotide linkers can be used to substitute the 5'-gaaa-2' loop shown in the figure. Zinzymes represent a non-limiting example of an enzymatic nucleic acid molecule that does not require a ribonucleotide (2'-OH) group within its own nucleic acid sequence for activity.

By 'DNAzyme' is meant, an enzymatic nucleic acid molecule that does not require the presence of a 2'-OH group within its own nucleic acid sequence for activity. In particular embodiments the enzymatic nucleic acid molecule can have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. DNAzymes can be synthesized chemically or expressed endogenously *in vivo*, by means of a single stranded DNA vector or equivalent thereof. An example of a DNAzyme is shown in **Figure 8** and is generally reviewed in Usman *et al.*, US patent No., 6,159,714; Chartrand *et al.*, 1995, *NAR* 23, 4092; Breaker *et al.*, 1995, *Chem. Bio.* 2, 655; Santoro *et al.*, 1997, *PNAS* 94, 4262; Breaker, 1999, *Nature Biotechnology*, 17, 422-423; and

Santoro *et. al.*, 2000, *J. Am. Chem. Soc.*, 122, 2433-39. The "10-23" DNAzyme motif is one particular type of DNAzyme that was evolved using *in vitro* selection, see Santoro *et al.*, *supra* and as generally described in Joyce *et al.*, US 5,807,718. Additional DNAzyme motifs can be selected for using techniques similar to those described in these references, and hence, are within the scope of the present invention.

By "sufficient length" is meant a nucleic acid molecule of the invention is long enough to provide the intended function under the expected condition. For example, a nucleic acid molecule of the invention needs to be of "sufficient length" to provide stable interaction with a target nucleic acid molecule under the expected binding conditions and environment. In another non-limiting example, for the binding arms of an enzymatic nucleic acid, "sufficient length" means that the binding arm sequence is long enough to provide stable binding to a target site under the expected reaction conditions and environment. The binding arms are not so long as to prevent useful turnover of the nucleic acid molecule.

By "stably interact" is meant interaction of an oligonucleotides with target nucleic acid (*e.g.*, by forming hydrogen bonds with complementary nucleotides in the target under physiological conditions) that is sufficient to the intended purpose (e.g., cleavage of target nucleic acid by an enzyme).

By "equivalent" RNA to VEGF, VEGFR1 and/or VEGFR2 is meant to include nucleic acid molecules having homology (partial or complete) to a nucleic acid encoding VEGF, VEGFR1 and/or VEGFR2 proteins or encoding proteins with similar function as VEGF, VEGFR1 and/or VEGFR2 proteins in various organisms, including human, rodent, primate, rabbit, pig, protozoans, fungi, plants, and other microorganisms and parasites. The equivalent nucleic acid sequence also includes, in addition to the coding region, regions such as 5'-untranslated region, 3'-untranslated region, introns, intron-exon junction and the like.

By "homology" is meant the nucleotide sequence of two or more nucleic acid molecules is partially or completely identical.

By "antisense nucleic acid", it is meant a non-enzymatic nucleic acid molecule that binds to target nucleic acid by means of RNA-RNA or RNA-DNA or RNA-PNA (protein nucleic acid; Egholm *et al.*, 1993 *Nature* 365, 566) interactions and alters the activity of the target nucleic acid (for a review, see Stein and Cheng, 1993 *Science* 261, 1004 and Woolf *et al.*, US patent No. 5,849,902). Typically, antisense molecules are complementary to a target sequence along a single contiguous sequence of the antisense molecule. However, in certain embodiments, an antisense molecule can bind to substrate such that the substrate molecule

forms a loop, and/or an antisense molecule can bind such that the antisense molecule forms a loop. Thus, an antisense molecule can be complementary to two (or even more) non-contiguous substrate sequences or two (or even more) non-contiguous sequence portions of an antisense molecule can be complementary to a target sequence or both. For a review of current antisense strategies, see Schmajuk *et al.*, 1999, *J. Biol. Chem.*, 274, 21783-21789, Delihas *et al.*, 1997, *Nature*, 15, 751-753, Stein *et al.*, 1997, *Antisense N. A. Drug Dev.*, 7, 151, Crooke, 2000, *Methods Enzymol.*, 313, 3-45; Crooke, 1998, *Biotech. Genet. Eng. Rev.*, 15, 121-157, Crooke, 1997, *Ad. Pharmacol.*, 40, 1-49. In addition, antisense DNA can be used to target nucleic acid by means of DNA-RNA interactions, thereby activating RNase H, which digests the target nucleic acid in the duplex. The antisense oligonucleotides can comprise one or more RNAse H activating region, which is capable of activating RNAse H cleavage of a target nucleic acid. Antisense DNA can be synthesized chemically or expressed via the use of a single stranded DNA expression vector or equivalent thereof.

By "RNase H activating region" is meant a region (generally greater than or equal to 4-25 nucleotides in length, preferably from 5-11 nucleotides in length) of a nucleic acid molecule capable of binding to a target nucleic acid to form a non-covalent complex that is recognized by cellular RNase H enzyme (see for example Arrow *et al.*, US 5,849,902; Arrow *et al.*, US 5,989,912). The RNase H enzyme binds to a nucleic acid molecule-target nucleic acid complex and cleaves the target nucleic acid sequence. The RNase H activating region comprises, for example, phosphodiester, phosphorothioate (preferably at least four of the nucleotides are phosphorothiote substitutions; more specifically, 4-11 of the nucleotides are phosphorothiote substitutions); phosphorodithioate, 5'-thiophosphate, or methylphosphonate backbone chemistry or a combination thereof. In addition to one or more backbone chemistries described above, the RNase H activating region can also comprise a variety of sugar chemistries. For example, the RNase H activating region can comprise deoxyribose, arabino, fluoroarabino or a combination thereof, nucleotide sugar chemistry. Those skilled in the art will recognize that the foregoing are non-limiting examples and that any combination of phosphate, sugar and base chemistry of a nucleic acid that supports the activity of RNase H enzyme is within the scope of the definition of the RNase H activating region and the instant invention.

By "2-5A antisense chimera" is meant an antisense oligonucleotide containing a 5'-phosphorylated 2'-5'-linked adenylate residue. These chimeras bind to target nucleic acid in a sequence-specific manner and activate a cellular 2-5A-dependent ribonuclease which, in turn, cleaves the target nucleic acid (Torrence *et al.*, 1993 *Proc. Natl. Acad. Sci. USA* 90, 1300;

Silverman *et al.*, 2000, *Methods Enzymol.*, 313, 522-533; Player and Torrence, 1998, *Pharmacol. Ther.*, 78, 55-113).

By "triplex forming oligonucleotides" is meant an oligonucleotide that can bind to a double-stranded polynucleotide, such as DNA, in a sequence-specific manner to form a triple-strand helix. Formation of such triple helix structure has been shown to inhibit transcription of the targeted gene (Duval-Valentin *et al.*, 1992 *Proc. Natl. Acad. Sci. USA* 89, 504; Fox, 2000, *Curr. Med. Chem.*, 7, 17-37; Praseuth *et. al.*, 2000, *Biochim. Biophys. Acta*, 1489, 181-206).

By "gene" it is meant a nucleic acid that encodes an RNA, for example, nucleic acid sequences including but not limited to structural genes encoding a polypeptide.

The term "complementarity" as used herein refers to the ability of a nucleic acid to form hydrogen bond(s) with another nucleic acid sequence by either traditional Watson-Crick or other non-traditional types. In reference to nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its target or complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., enzymatic nucleic acid cleavage, antisense or triple helix inhibition. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner *et al.*, 1987, *CSH Symp. Quant. Biol.* LII pp.123-133; Frier *et al.*, 1986, *Proc. Nat. Acad. Sci. USA* 83:9373-9377; Turner *et al.*, 1987, *J. Am. Chem. Soc.* 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule which can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, 10 out of 10 being 50%, 60%, 70%, 80%, 90%, and 100% complementary). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

By "RNA" is meant a molecule comprising at least one ribonucleotide residue. By "ribonucleotide" or "2'-OH" is meant a nucleotide with a hydroxyl group at the 2' position of a β-D-ribo-furanose moiety.

By "nucleic acid decoy molecule", or "decoy" as used herein is meant a nucleic acid molecule that mimics the natural binding domain for a ligand. The decoy therefore competes with the natural binding target for the binding of a specific ligand. For example, it has been shown that over-expression of HIV trans-activation response (TAR) RNA can act as a

"decoy" and efficiently binds HIV tat protein, thereby preventing it from binding to TAR sequences encoded in the HIV RNA (Sullenger et al., 1990, *Cell*, 63, 601-608).

By "aptamer" or "nucleic acid aptamer" as used herein is meant a nucleic acid molecule that binds specifically to a target molecule wherein the nucleic acid molecule has sequence that is distinct from sequence recognized by the target molecule in its natural setting. Alternately, an aptamer can be a nucleic acid molecule that binds to a target molecule where the target molecule does not naturally bind to a nucleic acid. The target molecule can be any molecule of interest. For example, the aptamer can be used to bind to a ligand binding domain of a protein, thereby preventing interaction of the naturally occurring ligand with the protein. Similarly, the nucleic acid molecules of the instant invention can bind to VEGFR1 or VEGFR2 receptors to block activity of the receptor. This is a non-limiting example and those in the art will recognize that other embodiments can be readily generated using techniques generally known in the art, see for example Gold *et al.*, US 5,475,096 and 5,270,163; Gold *et al.*, 1995, *Annu. Rev. Biochem.*, 64, 763; Brody and Gold, 2000, *J. Biotechnol.*, 74, 5; Sun, 2000, *Curr. Opin. Mol. Ther.*, 2, 100; Kusser, 2000, *J. Biotechnol.*, 74, 27; Hermann and Patel, 2000, *Science*, 287, 820; and Jayasena, 1999, *Clinical Chemistry*, 45, 1628.

The term "double stranded RNA" or "dsRNA" as used herein refers to a double stranded RNA molecule capable of RNA interference "RNAi", including short interfering RNA "siRNA" see for example Bass, 2001, *Nature*, 411, 428-429; Elbashir et al., 2001, *Nature*, 411, 494-498; and Kreutzer *et al.*, International PCT Publication No. WO 00/44895; Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646; Fire, International PCT Publication No. WO 99/32619; Plaetinck *et al.*, International PCT Publication No. WO 00/01846; Mello and Fire, International PCT Publication No. WO 01/29058; Deschamps-Depaillette, International PCT Publication No. WO 99/07409; and Li *et al.*, International PCT Publication No. WO 00/44914.

By "nucleic acid sensor molecule" or "allozyme" as used herein is meant a nucleic acid molecule comprising an enzymatic domain and a sensor domain, where the enzymatic nucleic acid domain's ability to catalyze a chemical reaction is dependent on the interaction with a target signaling molecule, such as a nucleic acid, polynucleotide, oligonucleotide, peptide, polypeptide, or protein, for example VEGF, VEGFR1 and/or VEGFR2. The introduction of chemical modifications, additional functional groups, and/or linkers, to the nucleic acid sensor molecule can provide enhanced catalytic activity of the nucleic acid sensor molecule, increased binding affinity of the sensor domain to a target nucleic acid, and/or improved nuclease/chemical stability of the nucleic acid sensor molecule, and are

hence within the scope of the present invention (see for example Usman *et al.*, US Patent Application No. 09/877,526, George *et al.*, US Patent Nos. 5,834,186 and 5,741,679, Shih *et al.*, US Patent No. 5,589,332, Nathan *et al.*, US Patent No 5,871,914, Nathan and Ellington, International PCT publication No. WO 00/24931, Breaker *et al.*, International PCT Publication Nos. WO 00/26226 and 98/27104, and Sullenger *et al.*, US Patent Application Serial No. 09/205,520).

By "sensor component" or "sensor domain" of the nucleic acid sensor molecule as used herein is meant, a nucleic acid sequence (e.g., RNA or DNA or analogs thereof) which interacts with a target signaling molecule, for example a nucleic acid sequence in one or more regions of a target nucleic acid molecule or more than one target nucleic acid molecule, and which interaction causes the enzymatic nucleic acid component of the nucleic acid sensor molecule to either catalyze a reaction or stop catalyzing a reaction. In the presence of target signaling molecule of the invention, such as VEGF, VEGFR1 and/or VEGFR2, the ability of the sensor component, for example, to modulate the catalytic activity of the nucleic acid sensor molecule, is inhibited or diminished. The sensor component can comprise recognition properties relating to chemical or physical signals capable of modulating the nucleic acid sensor molecule via chemical or physical changes to the structure of the nucleic acid sensor molecule. The sensor component can be derived from a naturally occurring nucleic acid binding sequence, for example, RNAs that bind to other nucleic acid sequences in vivo. Alternately, the sensor component can be derived from a nucleic acid molecule (aptamer) which is evolved to bind to a nucleic acid sequence within a target nucleic acid molecule (see for example Gold *et al.*, US 5,475,096 and 5,270,163). The sensor component can be covalently linked to the nucleic acid sensor molecule, or can be non-covalently associated. A person skilled in the art will recognize that all that is required is that the sensor component is able to selectively inhibit the activity of the nucleic acid sensor molecule to catalyze a reaction.

By "target molecule" or "target signaling molecule" is meant a molecule capable of interacting with a nucleic acid sensor molecule, specifically a sensor domain of a nucleic acid sensor molecule, in a manner that causes the nucleic acid sensor molecule to be active or inactive. The interaction of the signaling agent with a nucleic acid sensor molecule can result in modification of the enzymatic nucleic acid component of the nucleic acid sensor molecule via chemical, physical, topological, or conformational changes to the structure of the molecule, such that the activity of the enzymatic nucleic acid component of the nucleic acid sensor molecule is modulated, for example is activated or deactivated. Signaling agents can comprise target signaling molecules such as macromolecules, ligands, small molecules,

metals and ions, nucleic acid molecules including but not limited to RNA and DNA or analogs thereof, proteins, peptides, antibodies, polysaccharides, lipids, sugars, microbial or cellular metabolites, pharmaceuticals, and organic and inorganic molecules in a purified or unpurified form, for example VEGF, VEGFR1 and/or VEGFR2.

The term "triplex forming oligonucleotides" as used herein refers to an oligonucleotide that can bind to a double-stranded DNA in a sequence-specific manner to form a triple-strand helix. Formation of such a triple helix structure has been shown to inhibit transcription of a targeted gene (Duval-Valentin *et al.*, 1992 *Proc. Natl. Acad. Sci. USA* 89, 504; Fox, 2000, *Curr. Med. Chem.*, 7, 17-37; Praseuth *et. al.*, 2000, *Biochim. Biophys. Acta*, 1489, 181-206).

The nucleic acid molecules that modulate the expression of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 specific nucleic acids, represent a novel therapeutic approach to treat or control a variety of angiogenesis related disorders and conditions, including but not limited to tumor angiogenesis, cancers such as breast cancer, lung cancer, colorectal cancer, renal cancer, pancreatic cancer, or melanoma, or ocular indications such as diabetic retinopathy, or age related macular degeneration, and/or endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), and/or menopausal dysfunction. The nucleic acid molecules that modulate the expression of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 specific nucleic acids also represent a novel approach to control ovulation or embryonic implantation and therefore provide a novel means of birth control.

In one embodiment of the present invention, a nucleic acid molecule of the instant invention can be between 12 and 100 nucleotides in length. An exemplary enzymatic nucleic acid molecule of the invention is shown as Formula I and/or Formula II. For example, enzymatic nucleic acid molecules of the invention are preferably between 15 and 50 nucleotides in length, more preferably between 25 and 40 nucleotides in length, *e.g.*, 34, 36, or 38 nucleotides in length (for example see Jarvis *et al.*, 1996, *J. Biol. Chem.*, 271, 29107-29112). Exemplary DNAzymes of the invention are preferably between 15 and 40 nucleotides in length, more preferably between 25 and 35 nucleotides in length, *e.g.*, 29, 30, 31, or 32 nucleotides in length (see for example Santoro *et al.*, 1998, *Biochemistry*, 37, 13330-13342; Chartrand *et al.*, 1995, Nucleic Acids Research, 23, 4092-4096). Exemplary antisense molecules of the invention are preferably between 15 and 75 nucleotides in length, more preferably between 20 and 35 nucleotides in length, *e.g.*, 25, 26, 27, or 28 nucleotides in length (see for example Woolf *et al.*, 1992, *PNAS.*, 89, 7305-7309; Milner *et al.*, 1997, *Nature Biotechnology*, 15, 537-541). Exemplary triplex forming oligonucleotide molecules of the invention are preferably between 10 and 40 nucleotides in length, more preferably

between 12 and 25 nucleotides in length, *e.g.*, 18, 19, 20, or 21 nucleotides in length (see for example Maher *et al.*, 1990, *Biochemistry*, 29, 8820-8826; Strobel and Dervan, 1990, *Science*, 249, 73-75). Those skilled in the art will recognize that all that is required is that the nucleic acid molecule be of length and conformation sufficient and suitable for the nucleic acid molecule to catalyze a reaction contemplated herein. The length of the nucleic acid molecules of the instant invention are not limiting within the general limits stated.

In a preferred embodiment, a nucleic acid molecule that modulates, for example, down-regulates, VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 replication or expression comprises between 8 and 100 bases complementary to a nucleic acid molecule of VEGFR1 and/or VEGFR2. More preferably, a nucleic acid molecule that modulates VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 replication or expression comprises between 14 and 24 bases complementary to a nucleic acid molecule of VEGFR1 and/or VEGFR2.

The invention provides a method for producing a class of nucleic acid–based gene modulating agents which exhibit a high degree of specificity for the nucleic acid of a desired target. For example, a nucleic acid molecule of the invention is preferably targeted to a highly conserved sequence region of target nucleic acids encoding VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 (specifically VEGF, VEGFR1 and/or VEGFR2 genes) such that specific treatment of a disease or condition can be provided with either one or several nucleic acid molecules of the invention. Such nucleic acid molecules can be delivered exogenously to specific tissue or cellular targets as required. Alternatively, the nucleic acid molecules can be expressed from DNA and/or RNA vectors that are delivered to specific cells.

As used in herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism. The cell can, for example, be *in vitro*, e.g., in cell culture, or present in a multicellular organism, including,, e.g., birds, plants and mammals such as humans, cows, sheep, apes, monkeys, swine, dogs, and cats. The cell may be prokaryotic (e.g., bacterial cell) or eukaryotic (e.g., mammalian or plant cell).

By "VEGFR1 and/or VEGFR2 proteins" is meant, protein receptor or a mutant protein derivative thereof, having vascular endothelial growth factor receptor activity, for example, having the ability to bind vascular endothelial growth factor and/or having tyrosine kinase activity.

By "highly conserved sequence region" is meant, a nucleotide sequence of one or more regions in a target gene does not vary significantly from one generation to the other or from one biological system to the other.

"Angiogenesis" refers to formation of new blood vessels which is an essential process in reproduction, development and wound repair. "Tumor angiogenesis" refers to the induction of the growth of blood vessels from surrounding tissue into a solid tumor. Tumor growth and tumor metastasis are dependent on angiogenesis (for a review see Folkman, 1985 *supra*; Folkman 1990 *J. Natl. Cancer Inst.*, 82, 4; Folkman and Shing, 1992 *J. Biol. Chem.* 267, 10931).

Angiogenesis plays an important role in other diseases such as arthritis wherein new blood vessels have been shown to invade the joints and degrade cartilage (Folkman and Shing, *supra*).

"Retinopathy" refers to inflammation of the retina and/or degenerative condition of the retina which may lead to occlusion of the retina and eventual blindness. In "diabetic retinopathy" angiogenesis causes the capillaries in the retina to invade the vitreous resulting in bleeding and blindness which is also seen in neonatal retinopathy (for a review see Folkman, 1985 *supra*; Folkman 1990 *supra;* Folkman and Shing, 1992 *supra*).

Nucleic acid-based inhibitors of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2, expression are useful for the prevention, treatment, and/or control of angiogenesis related disorders and conditions, including but not limited to, tumor angiogenesis, cancers such as breast cancer, lung cancer, colorectal cancer, renal cancer, pancreatic cancer, or melanoma, or ocular indications such as diabetic retinopathy, or age related macular degeneration, and/or endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), menopausal dysfunction, and other diseases or conditions that are related to or will respond to the levels of VEGF, VEGFR1 and/or VEGFR2 in a cell or tissue, alone or in combination with other therapies. The reduction of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 expression (specifically VEGF, VEGFR1 and/or VEGFR2 gene RNA levels) and thus reduction in the level of the respective protein relieves, to some degree, the symptoms of the disease or condition. Nucleic acid-based inhibitors of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 expression are also useful as birth control agents, for example by inhibition of ovulation or embryonic uterine implantation.

The nucleic acid molecules of the invention can be added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic acid complexes can be locally administered to relevant tissues ex vivo, or in vivo through injection or infusion pump, with or without their incorporation in biopolymers. In preferred embodiments, the nucleic acid inhibitors comprise sequences, which are complementary to polynucleotides, for example DNA and RNA, having VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 sequence.

Triplex molecules of the invention can be provided targeted to DNA target regions, and containing the DNA equivalent of a target sequence or a sequence complementary to the specified target (substrate) sequence. Antisense molecules typically are complementary to a target sequence along a single contiguous sequence of the antisense molecule. However, in certain embodiments, an antisense molecule can bind to substrate such that the substrate molecule forms a loop, and/or an antisense molecule can bind such that the antisense molecule forms a loop. Thus, the antisense molecule can be complementary to two (or even more) non-contiguous substrate sequences or two (or even more) non-contiguous sequence portions of an antisense molecule can be complementary to a target sequence or both.

By "consists essentially of" is meant that the active nucleic acid molecule of the invention, for example, an enzymatic nucleic acid molecule, contains an enzymatic center or core equivalent to those in the examples, and binding arms able to bind nucleic acid such that cleavage at the target site occurs. Other sequences can be present which do not interfere with such cleavage. Thus, a core region can, for example, include one or more loop, stem-loop structure, or linker which does not prevent enzymatic activity. Thus, a particular region of a nucleic acid molecule of the invention can be such a loop, stem-loop, nucleotide linker, and/or non-nucleotide linker and can be represented generally as sequence "X". Thus, a core region may, for example, include one or more loop or stem-loop structures which do not prevent enzymatic activity. For example, a core sequence for a hammerhead enzymatic nucleic acid can comprise a conserved sequence, such as 5'-CUGAUGAG-3' and 5'-CGAA-3' connected by "X", where X is 5'-<u>GCCGUUAGGC</u>-3' (SEQ ID NO 5979), or any other Stem II region known in the art, or a nucleotide and/or non-nucleotide linker. Similarly, for other nucleic acid molecules of the instant invention, such as Inozyme, G-cleaver, amberzyme, zinzyme, DNAzyme, antisense, 2-5A antisense, triplex forming nucleic acid, aptamers, decoy nucleic acids, dsRNA or siRNA, other sequences or non-nucleotide linkers can be present that do not interfere with the function of the nucleic acid molecule.

Sequence X can be a linker of ≥ 2 nucleotides in length, preferably 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 26, 30, where the nucleotides can preferably be internally base-paired to form a stem of preferably ≥ 2 base pairs. Alternatively or in addition, sequence X can be a non-nucleotide linker. In yet another embodiment, the nucleotide linker X can be a nucleic acid aptamer, such as an ATP aptamer, HIV Rev aptamer (RRE), HIV Tat aptamer (TAR) and others (for a review see Gold *et al.*, 1995, *Annu. Rev. Biochem.*, 64, 763; and Szostak & Ellington, 1993, in *The RNA World*, ed. Gesteland and Atkins, pp. 511, CSH Laboratory Press). A nucleic acid aptamer includes a nucleic acid sequence capable of interacting with a ligand. The ligand can be any natural or a synthetic molecule, including but not limited to a resin, metabolites, nucleosides, nucleotides, drugs, toxins, transition state analogs, peptides, lipids, proteins, amino acids, nucleic acid molecules, hormones, carbohydrates, receptors, cells, viruses, bacteria and others.

In yet another embodiment, the non-nucleotide linker X is as defined herein. The term "non-nucleotide" as used herein include either abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, or polyhydrocarbon compounds. Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res.* 1990, *18*:6353 and *Nucleic Acids Res.* 1987, *15*:3113; Cload and Schepartz, *J. Am. Chem. Soc.* 1991, *113*:6324; Richardson and Schepartz, *J. Am. Chem. Soc.* 1991, *113*:5109; Ma *et al.*, *Nucleic Acids Res.* 1993, *21*:2585 and *Biochemistry* 1993, *32*:1751; Durand *et al.*, *Nucleic Acids Res.* 1990, *18*:6353; McCurdy *et al.*, *Nucleosides & Nucleotides* 1991, *10*:287; Jschke *et al.*, *Tetrahedron Lett.* 1993, *34*:301; Ono *et al.*, *Biochemistry* 1991, *30*:9914; Arnold *et al.*, International Publication No. WO 89/02439; Usman *et al.*, International Publication No. WO 95/06731; Dudycz *et al.*, International Publication No. WO 95/11910 and Ferentz and Verdine, *J. Am. Chem. Soc.* 1991, *113*:4000, all hereby incorporated by reference herein.

A "non-nucleotide" further means any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound can be abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine. Thus, in one embodiment, the invention features an enzymatic nucleic acid molecule having one or more non-nucleotide moieties, and having enzymatic activity to cleave an RNA or DNA molecule.

In another aspect of the invention, nucleic acid molecules that interact with target nucleic acid molecules and down-regulate VEGF and/or VEGFr, such as VEGFR1 and/or

VEGFR2 (specifically VEGF, VEGFR1 and/or VEGFR2 gene) activity are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors are preferably DNA plasmids or viral vectors. Enzymatic nucleic acid molecule or antisense expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the enzymatic nucleic acid molecules or antisense are delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of enzymatic nucleic acid molecules or antisense. Such vectors can be repeatedly administered as necessary. Once expressed, the enzymatic nucleic acid molecules or antisense bind to the target nucleic acid and down-regulate its function or expression. Delivery of enzymatic nucleic acid molecule or antisense expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that would allow for introduction into the desired target cell. Antisense DNA can be expressed via the use of a single stranded DNA intracellular expression vector.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

By "subject" or "patient" is meant an organism, which is a donor or recipient of explanted cells, or the cells themselves. "Subject" or "Patient" also refers to an organism to which the nucleic acid molecules of the invention can be administered. Preferably, a subject or patient is a mammal or mammalian cells. More preferably, a subject or patient is a human or human cells.

By "enhanced enzymatic activity" is meant to include activity measured in cells and/or in vivo where the activity is a reflection of both the catalytic activity and the stability of the nucleic acid molecules of the invention. In this invention, the product of these properties can be increased *in vivo* compared to an all RNA enzymatic nucleic acid or all DNA enzyme. In some cases, the activity or stability of the nucleic acid molecule can be decreased (i.e., less than ten-fold), but the overall activity of the nucleic acid molecule is enhanced, *in vivo*.

The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed above. For example, to treat a disease or condition associated with the levels of VEGFR1 and/or VEGFR2, the patient can be treated, or other appropriate cells can be treated, as is evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment.

In a further embodiment, the described molecules of the invention can be used in combination with other known treatments to treat conditions or diseases discussed above. For example, the described molecules can be used in combination with one or more known therapeutic agents to treat angiogenesis related disorders and conditions, including but not limited to tumor angiogenesis, cancers such as breast cancer, lung cancer, colorectal cancer, renal cancer, pancreatic cancer, or melanoma, or ocular indications such as diabetic retinopathy, or age related macular degeneration, and/or endometriosis, birth control, endometrial tumors, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), menopausal dysfunction, endometrial carcinoma, and/or other diseases or conditions which respond to the modulation of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 expression.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Brief Description of the Drawings

Figure 1 shows a secondary structure model of ANGIOZYME™ ribozyme bound to its RNA target.

Figure 2 shows a time course of inhibition of primary tumor growth following systemic administration of ANGIOZYME™ in the LLC mouse model.

Figure 3 shows inhibition of primary tumor growth following systemic administration of ANGIOZYME™ according to a certain dosing regimen in the LLC mouse model.

Figure 4 shows a dose-dependent inhibition of tumor metastases following systemic administration of ANGIOZYME™ in a mouse colorectal model.

Figure 5 is a graph showing the plasma concentration profile of ANGIOZYME™ after a single subcutaneous (SC) dose of 10, 30, 100 or 300 mg/m^2.

Figure 6 shows examples of chemically stabilized ribozyme motifs. **HH Rz**, represents hammerhead ribozyme motif (Usman *et al.*, 1996, *Curr. Op. Struct. Bio.*, 1, 527); **NCH Rz** represents the NCH ribozyme motif (Ludwig *et al.*, International PCT Publication No. WO 98/58058 and US Patent Application Serial No. 08/878,640); **G-Cleaver**, represents G-cleaver ribozyme motif (Kore *et al.*, 1998, *Nucleic Acids Research* 26, 4116-4120, Eckstein *et*

al., US 6,127,173). **N** or **n**, represent independently a nucleotide which can be same or different and have complementarity to each other; **rI**, represents ribo-Inosine nucleotide; arrow indicates the site of cleavage within the target. Position 4 of the HH Rz and the NCH Rz is shown as having 2'-*C*-allyl modification, but those skilled in the art will recognize that this position can be modified with other modifications well known in the art, so long as such modifications do not significantly inhibit the activity of the ribozyme.

Figure 7 shows an example of a Zinzyme A ribozyme motif that is chemically stabilized (see for example Beigelman *et al.*, International PCT publication No. WO 99/55857 and US Patent Application Serial No. 09/918,728).

Figure 8 shows an example of a DNAzyme motif described by Santoro *et al.*, 1997, *PNAS*, 94, 4262 and Joyce *et al.*, US 5,807,718 .

Figure 9 shows data demonstrating the inhibition of soluble VEGFR1 in a clinical study using ANGIOZYME (SEQ ID NO: 5977) .

Figure 10 shows an generalized outline for the mouse model of proliferative retinopathy showing the points of ribozyme administration.

Figure 11 shows a graph demonstrating the efficacy of a VEGF-receptor-targeted enzymatic nucleic acid molecule in a mouse model of proliferative retinopathy.

Detailed Description of the Invention

Nucleic Acid Molecules and Mechanism of Action

Enzymatic Nucleic Acid: Several varieties of naturally-occurring enzymatic nucleic acids are presently known. In addition, several *in vitro* selection (evolution) strategies (Orgel, 1979, *Proc. R. Soc. London*, B 205, 435) have been used to evolve new nucleic acid catalysts capable of catalyzing cleavage and ligation of phosphodiester linkages (Joyce, 1989, *Gene*, 82, 83-87; Beaudry *et al.*, 1992, *Science* 257, 635-641; Joyce, 1992, *Scientific American* 267, 90-97; Breaker *et al.*, 1994, *TIBTECH* 12, 268; Bartel *et al.*,1993, *Science* 261:1411-1418; Szostak, 1993, *TIBS* 17, 89-93; Kumar *et al.*, 1995, *FASEB J.*, 9, 1183; Breaker, 1996, *Curr. Op. Biotech.*, 7, 442; Santoro *et al.*, 1997, *Proc. Natl. Acad. Sci.*, 94, 4262; Tang *et al.*, 1997, *RNA* 3, 914; Nakamaye & Eckstein, 1994, *supra*; Long & Uhlenbeck, 1994, supra; Ishizaka *et al.*, 1995, *supra*; Vaish *et al.*, 1997, *Biochemistry* 36, 6495; all of these are incorporated by reference herein). Each can catalyze a series of reactions including the hydrolysis of

phosphodiester bonds in *trans* (and thus can cleave other nucleic acid molecules) under physiological conditions.

The enzymatic nature of an enzymatic nucleic acid molecule has significant advantages, one advantage being that the concentration of enzymatic nucleic acid molecule necessary to affect a therapeutic treatment is lower. This advantage reflects the ability of the enzymatic nucleic acid molecule to act enzymatically. Thus, a single enzymatic nucleic acid molecule is able to cleave many molecules of target nucleic acid. In addition, the enzymatic nucleic acid molecule is a highly specific inhibitor, with the specificity of inhibition depending not only on the base-pairing mechanism of binding to the target nucleic acid , but also on the mechanism of target nucleic acid cleavage. Single mismatches, or base-substitutions, near the site of cleavage can be chosen to completely eliminate catalytic activity of a enzymatic nucleic acid molecule.

Nucleic acid molecules having an endonuclease enzymatic activity are able to repeatedly cleave other separate nucleic acid molecules in a nucleotide base sequence-specific manner. With the proper design, such enzymatic nucleic acid molecules can be targeted to RNA transcripts, and achieve efficient cleavage *in vitro* (Zaug *et al.*, 324, *Nature* 429 1986; Uhlenbeck, 1987 *Nature* 328, 596; Kim *et al.*, 84 *Proc. Natl. Acad. Sci. USA* 8788, 1987; Dreyfus, 1988, *Einstein Quart. J. Bio. Med.*, 6, 92; Haseloff and Gerlach, 334 *Nature* 585, 1988; Cech, 260 *JAMA* 3030, 1988; and Jefferies *et al.*, 17 *Nucleic Acids Research* 1371, 1989; Santoro *et al.*, 1997 *supra*).

Because of their sequence specificity, *trans*-cleaving enzymatic nucleic acid molecules can be used as therapeutic agents for human disease (Usman & McSwiggen, 1995 *Ann. Rep. Med. Chem.* 30, 285-294; Christoffersen and Marr, 1995 *J. Med. Chem.* 38, 2023-2037). Enzymatic nucleic acid molecules can be designed to cleave specific nucleic acid targets within the background of cellular nucleic acid. Such a cleavage event renders the nucleic acid non-functional and abrogates protein expression from that nucleic acid. In this manner, synthesis of a protein associated with a disease state can be selectively inhibited (Warashina *et al.*, 1999, *Chemistry and Biology*, 6, 237-250).

Enzymatic nucleic acid molecules of the invention that are allosterically regulated ("allozymes") can be used to down-regulate VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2, expression. These allosteric enzymatic nucleic acids or allozymes (see for example Usman *et al.*, US Patent Application No. 09/877,526, George *et al.*, US Patent Nos. 5,834,186 and 5,741,679, Shih *et al.*, US Patent No. 5,589,332, Nathan *et al.*, US Patent No 5,871,914, Nathan and Ellington, International PCT publication No. WO 00/24931, Breaker

et al., International PCT Publication Nos. WO 00/26226 and 98/27104, and Sullenger *et al.*, US Patent Application Serial No. 09/205,520) are designed to respond to a signaling agent, for example, mutant VEGFR1 and/or VEGFR2 protein, wild-type VEGFR1 and/or VEGFR2 protein, mutant VEGFR1 and/or VEGFR2 RNA, wild-type VEGFR1 and/or VEGFR2 RNA, other proteins and/or RNAs involved in VEGF signal transduction, compounds, metals, polymers, molecules and/or drugs that are targeted to VEGFR1 and/or VEGFR2 expression, which in turn modulates the activity of the enzymatic nucleic acid molecule. In response to interaction with a predetermined signaling agent, the activity of the allosteric enzymatic nucleic acid is activated or inhibited such that the expression of a particular target is selectively down-regulated. The target can comprise wild-type VEGFR1 and/or VEGFR2, mutant VEGFR1 and/or VEGFR2, and/or a predetermined component of the VEGF signal transduction pathway. In a specific example, allosteric enzymatic nucleic acid molecules that are activated by interaction with a RNA encoding VEGF protein are used as therapeutic agents *in vivo*. The presence of RNA encoding the VEGF protein activates the allosteric enzymatic nucleic acid molecule that subsequently cleaves the RNA encoding a VEGFR1 and/or VEGFR2 protein resulting in the inhibition of VEGFR1 and/or VEGFR2 protein expression.

In another non-limiting example, an allozyme can be activated by a VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 protein, peptide, or mutant polypeptide that causes the allozyme to inhibit the expression of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 genes, by, for example, cleaving RNA encoded by VEGF, VEGFR1 and/or VEGFR2 gene. In this non-limiting example, the allozyme acts as a decoy to inhibit the function of VEGF, VEGFR1 and/or VEGFR2 and also inhibit the expression of VEGF, VEGFR1 and/or VEGFR2 once activated by the VEGF, VEGFR1 and/or VEGFR2 protein.

Antisense: Antisense molecules can be modified or unmodified RNA, DNA, or mixed polymer oligonucleotides and primarily function by specifically binding to matching sequences resulting in inhibition of peptide synthesis (Wu-Pong, Nov 1994, *BioPharm*, 20-33). The antisense oligonucleotide binds to target RNA by Watson Crick base-pairing and blocks gene expression by preventing ribosomal translation of the bound sequences either by steric blocking or by activating RNase H enzyme. Antisense molecules can also alter protein synthesis by interfering with RNA processing or transport from the nucleus into the cytoplasm (Mukhopadhyay & Roth, 1996, *Crit. Rev. in Oncogenesis* 7, 151-190).

In addition, binding of single stranded DNA to RNA can result in nuclease degradation of the heteroduplex (Wu-Pong, *supra*; Crooke, *supra*). To date, the only backbone modified

DNA chemistry which act as substrates for RNase H are phosphorothioates, phosphorodithioates, and borontrifluoridates. Recently it has been reported that 2'-arabino and 2'-fluoro arabino- containing oligos can also activate RNase H activity.

A number of antisense molecules have been described that utilize novel configurations of chemically modified nucleotides, secondary structure, and/or RNase H substrate domains (Woolf *et al.,* International PCT Publication No. WO 98/13526; Thompson *et al.,* International PCT Publication No. WO 99/54459; Hartmann *et al.,* USSN 60/101,174 which was filed on September 21, 1998) all of these are incorporated by reference herein in their entirety.

In addition, antisense deoxyoligoribonucleotides can be used to target RNA by means of DNA-RNA interactions, thereby activating RNase H, which digests the target RNA in the duplex. Antisense DNA can be expressed via the use of a single stranded DNA intracellular expression vector or equivalents and variations thereof.

Triplex Forming Oligonucleotides (TFO): Single stranded DNA can be designed to bind to genomic DNA in a sequence specific manner. TFOs are comprised of pyrimidine-rich oligonucleotides which bind DNA helices through Hoogsteen Base-pairing (Wu-Pong, *supra*). The resulting triple helix composed of the DNA sense, DNA antisense, and TFO disrupts RNA synthesis by RNA polymerase. The TFO mechanism can result in gene expression or cell death since binding can be irreversible (Mukhopadhyay & Roth, *supra*).

2-5A Antisense Chimera: The 2-5A system is an interferon mediated mechanism for RNA degradation found in higher vertebrates (Mitra *et al.,* 1996, *Proc Nat Acad Sci USA* 93, 6780-6785). Two types of enzymes, 2-5A synthetase and RNase L, are required for RNA cleavage. The 2-5A synthetases require double stranded RNA to form 2'-5' oligoadenylates (2-5A). 2-5A then acts as an allosteric effector for utilizing RNase L which has the ability to cleave single stranded RNA. The ability to form 2-5A structures with double stranded RNA makes this system particularly useful for inhibition of viral replication.

(2'-5') oligoadenylate structures can be covalently linked to antisense molecules to form chimeric oligonucleotides capable of RNA cleavage (Torrence, *supra*). These molecules putatively bind and activate a 2-5A dependent RNase, the oligonucleotide/enzyme complex then binds to a target RNA molecule which can then be cleaved by the RNase enzyme.

RNAi: Double-stranded RNAs can suppress expression of homologous genes through an evolutionarily conserved process named RNA interference (RNAi) or post-transcriptional gene silencing (PTGS). One mechanism underlying silencing is the degradation of target mRNAs by an RNP complex, which contains short interfering RNAs (siRNAs) as guides to substrate selection. Short interfering RNAs are typically 21 to 23 nucleotides in length. A bidentate nuclease called Dicer has been implicated as the protein responsible for siRNA production. For example, a double-stranded RNA (dsRNA) matching a gene sequence is synthesized *in vitro* and introduced into a cell. The dsRNA feeds into a biological pathway and is broken into short pieces of short interfering (si) RNAs. With the help of cellular enzymes such as Dicer, the siRNA triggers the degradation of the messenger RNA that matches its sequence (see for example Tuschl *et al.*, International PCT Publication No. WO 01/75164; Bass, 2001, *Nature*, 411, 428-429; Elbashir et al., 2001, *Nature*, 411, 494-498; and Kreutzer *et al.*, International PCT Publication No. WO 00/44895).

Target sites

Targets for useful nucleic acid molecules of the invention, such as enzymatic nucleic acid molecules, dsRNA, and antisense nucleic acids can be determined as disclosed in Draper *et al.*, WO 93/23569; Sullivan *et al.*, WO 93/23057; Thompson *et al.*, WO 94/02595; Draper *et al.*, WO 95/04818; McSwiggen *et al.*, US Patent No. 5,525,468, and hereby incorporated by reference herein in totality. Other examples include the following PCT applications, which concern inactivation of expression of disease-related genes: WO 95/23225, WO 95/13380, WO 94/02595, incorporated by reference herein. Rather than repeat the guidance provided in those documents here, below are provided specific examples of such methods, not limiting to those in the art. Enzymatic nucleic acid molecules and antisense to such targets are designed as described in those applications and synthesized to be tested *in vitro* and *in vivo*, as also described. The sequences of human VEGF, VEGFR1 and/or VEGFR2 RNAs are screened for optimal nucleic acid target sites using a computer-folding algorithm. Potential nucleic acid binding/cleavage sites are identified. While human sequences can be screened and nucleic acid molecules thereafter designed, as discussed in Stinchcomb *et al.*, WO 95/23225, mouse targeted enzymatic nucleic acid molecules can be useful to test efficacy of action of the nucleic acid molecule prior to testing in humans.

Nucleic acid molecule binding/cleavage sites are identified, for example enzymatic nucleic acid, antisense, and dsRNA mediated binding sites are chosen. For enzymatic nucleic acid molecules of the invention, the nucleic acid molecules are individually analyzed by computer folding (Jaeger *et al.*, 1989 *Proc. Natl. Acad. Sci. USA*, 86, 7706) to assess whether

the sequences fold into the appropriate secondary structure. Those nucleic acid molecules with unfavorable intramolecular interactions such as between the binding arms and the catalytic core can be eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity.

Nucleic acids, such as antisense, RNAi, and/or enzymatic nucleic acid molecule binding/cleavage sites are identified and are designed to anneal to various sites in the nucleic acid target. The binding arms of enzymatic nucleic acid molecules of the invention are complementary to the target site sequences described above. Antisense and RNAi sequences are designed to have partial or complete complementarity to the nucleic acid target. The nucleic acid molecules can be chemically synthesized. The method of synthesis used follows the procedure for normal DNA/RNA synthesis as described below and in Usman *et al.*, 1987 *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.*, 1990 *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677-2684; Caruthers *et al.*, 1992, *Methods in Enzymology* 211,3-19.

Synthesis of Nucleic acid Molecules

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small refers to nucleic acid motifs less than about 100 nucleotides in length, preferably less than about 80 nucleotides in length, and more preferably less than about 50 nucleotides in length; *e.g.*, antisense oligonucleotides, enzymatic nucleic acids, aptamers, allozymes, decoys, siRNA etc.) are preferably used for exogenous delivery. The simple structure of these molecules increases the ability of the nucleic acid to invade targeted regions of RNA structure. Exemplary molecules of the instant invention are chemically synthesized, and others can similarly be synthesized.

DNA Oligonucleotides are synthesized using protocols known in the art as described in Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19, Thompson *et al.*, International PCT Publication No. WO 99/54459, Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684, Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, Brennan *et al.*, 1998, *Biotechnol Bioeng.*, 61, 33-45, and Brennan, US patent No. 6,001,311. All of these references are incorporated herein by reference. The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 2.5 min coupling step for 2'-O-methylated nucleotides and a 45 sec coupling step for 2'-deoxy nucleotides. **Table II**

outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 µmol scale can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 µL of 0.11 M = 6.6 µmol) of 2'-O-methyl phosphoramidite and a 105-fold excess of S-ethyl tetrazole (60 µL of 0.25 M = 15 µmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 22-fold excess (40 µL of 0.11 M = 4.4 µmol) of deoxy phosphoramidite and a 70-fold excess of S-ethyl tetrazole (40 µL of 0.25 M = 10 µmol) can be used in each coupling cycle of deoxy residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include; detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); and oxidation solution is 16.9 mM I_2, 49 mM pyridine, 9% water in THF (PERSEPTIVE™). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide, 0.05 M in acetonitrile) is used.

Deprotection of the DNA polynucleotides is performed as follows: the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to –20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H2O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder.

The method of synthesis used for RNA oligonucleotides including certain nucleic acid molecules of the invention follows the procedure as described in Usman *et al.*, 1987, *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.*, 1990, *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684 Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 µmol scale protocol with a 7.5 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides. **Table II** outlines the amounts and the

contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M = 6.6 μmol) of 2'-O-methyl phosphoramidite and a 75-fold excess of S-ethyl tetrazole (60 μL of 0.25 M = 15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 66-fold excess (120 μL of 0.11 M = 13.2 μmol) of alkylsilyl (ribo) protected phosphoramidite and a 150-fold excess of S-ethyl tetrazole (120 μL of 0.25 M = 30 μmol) can be used in each coupling cycle of ribo residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include; detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution is 16.9 mM I_2, 49 mM pyridine, 9% water in THF (PERSEPTIVE™). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide0.05 M in acetonitrile) is used.

Deprotection of the RNA is performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to –20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H2O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder. The base deprotected oligoribonucleotide is resuspended in anhydrous TEA/HF/NMP solution (300 μL of a solution of 1.5 mL N-methylpyrrolidinone, 750 μL TEA and 1 mL TEA•3HF to provide a 1.4 M HF concentration) and heated to 65 °C. After 1.5 h, the oligomer is quenched with 1.5 M NH_4HCO_3.

Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO: 1/1 (0.8 mL) at 65 °C for 15 min. The vial is brought to r.t. TEA•3HF (0.1 mL) is added and the vial is heated at 65 °C for 15 min. The sample is cooled at –20 °C and then quenched with 1.5 M NH_4HCO_3.

For purification of the trityl-on oligomers, the quenched NH_4HCO_3 solution is loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing the loaded cartridge with water, the RNA is detritylated with 0.5% TFA for 13 min. The cartridge is then washed again with water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide is then eluted with 30% acetonitrile.

Inactive hammerhead ribozymes or binding attenuated control (BAC) oligonucleotides) are synthesized by substituting a U for G_5 and a U for A_{14} (numbering from Hertel, K. J., *et al.*, 1992, *Nucleic Acids Res.*, 20, 3252). Similarly, one or more nucleotide substitutions can be introduced in other enzymatic nucleic acid molecules to inactivate the molecule and such molecules can serve as a negative control.

The average stepwise coupling yields are typically >98% (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96 well format, all that is important is the ratio of chemicals used in the reaction.

Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example by ligation (Moore *et al.*, 1992, *Science* 256, 9923; Draper *et al.*, International PCT publication No. WO 93/23569; Shabarova *et al.*, 1991, *Nucleic Acids Research* 19, 4247; Bellon *et al.*, 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon *et al.*, 1997, *Bioconjugate Chem.* 8, 204).

Preferably, the nucleic acid molecules of the present invention are modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-*C*-allyl, 2'-flouro, 2'-*O*-methyl, 2'-H (for a review see Usman and Cedergren, 1992, *TIBS* 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163). Ribozymes are purified by gel electrophoresis using general methods or are purified by high pressure liquid chromatography (HPLC; See Wincott *et al.*, Supra, the totality of which is hereby incorporated herein by reference) and are re-suspended in water.

<u>Optimizing Activity of the nucleic acid molecule of the invention.</u>

Chemically synthesizing nucleic acid molecules with modifications (base, sugar and/or phosphate) that prevent their degradation by serum ribonucleases can increase their potency (see *e.g.*, Eckstein *et al.*, International Publication No. WO 92/07065; Perrault *et al.*, 1990 *Nature* 344, 565; Pieken et al., 1991, *Science* 253, 314; Usman and Cedergren, 1992, *Trends*

in Biochem. Sci. 17, 334; Usman *et al.*, International Publication No. WO 93/15187; and Rossi *et al.*, International Publication No. WO 91/03162; Sproat, US Patent No. 5,334,711; Gold *et al.*, US 6,300,074; and Burgin *et al., supra;* all of which are incorporated by reference herein). Modifications which enhance their efficacy in cells, and removal of bases from nucleic acid molecules to shorten oligonucleotide synthesis times and reduce chemical requirements are desired. (All these publications are hereby incorporated by reference herein).

There are several examples in the art describing sugar, base and phosphate modifications that can be introduced into nucleic acid molecules with significant enhancement in their nuclease stability and efficacy. For example, oligonucleotides are modified to enhance stability and/or enhance biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-*C*-allyl, 2'-flouro, 2'-*O*-methyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992, *TIBS.* 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163; Burgin *et al.*, 1996, *Biochemistry*, 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein *et al., International Publication* PCT No. WO 92/07065; Perrault *et al. Nature,* 1990, *344*, 565-568; Pieken *et al. Science,* 1991, *253*, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.* , 1992, *17*, 334-339; Usman *et al. International Publication* PCT No. WO 93/15187; Sproat, *US Patent* No. 5,334,711 and Beigelman *et al.*, 1995, *J. Biol. Chem.*, 270, 25702; Beigelman *et al.*, International PCT publication No. WO 97/26270; Beigelman *et al.*, US Patent No. 5,716,824; Usman *et al.*, US patent No. 5,627,053; Woolf *et al.*, International PCT Publication No. WO 98/13526; Thompson *et al.*, USSN 60/082,404 which was filed on April 20, 1998; Karpeisky *et al.*, 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, *Biopolymers (Nucleic acid Sciences)*, 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*, 67, 99-134; and Burlina *et al.*, 1997, *Bioorg. Med. Chem.*, 5, 1999-2010; all of the references are hereby incorporated in their totality by reference herein). Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into ribozymes without inhibiting catalysis, and are incorporated by reference herein. In view of such teachings, similar modifications can be used as described herein to modify the nucleic acid molecules of the instant invention.

While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorothioate, and/or 5'-methylphosphonate linkages improves stability, too many of these modifications can cause some toxicity. Therefore when designing nucleic acid molecules the amount of these internucleotide linkages should be minimized.

The reduction in the concentration of these linkages should lower toxicity resulting in increased efficacy and higher specificity of these molecules.

Nucleic acid molecules having chemical modifications that maintain or enhance activity are provided. Such nucleic acid is also generally more resistant to nucleases than unmodified nucleic acid. Thus, in a cell and/or *in vivo* the activity may not be significantly lowered. Therapeutic nucleic acid molecules delivered exogenously are optimally stable within cells until translation of the target RNA has been inhibited long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Clearly, nucleic acid molecules must be resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of RNA and DNA (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677; Caruthers *et al.*, 1992, *Methods in Enzymology* 211,3-19 (incorporated by reference herein) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

In one embodiment, nucleic acid molecules of the invention include one or more G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein the modifications confer the ability to hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J. Am. Chem. Soc.*, 120, 8531-8532. A single G-clamp analog substitution within an oligonucleotide can result in substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in nucleic acid molecules of the invention results in both enhanced affinity and specificity to nucleic acid targets. In another embodiment, nucleic acid molecules of the invention include one or more LNA "locked nucleic acid" nucleotides such as a 2', 4'-C mythylene bicyclo nucleotide (see for example Wengel *et al.*, International PCT Publication No. WO 00/66604 and WO 99/14226).

In another embodiment, the invention features conjugates and/or complexes of nucleic acid molecules targeting VEGF receptors such as VEGFR1 and/or VEGFR2. Such conjugates and/or complexes can be used to facilitate delivery of molecules into a biological system, such as cells. The conjugates and complexes provided by the instant invention can impart therapeutic activity by transferring therapeutic compounds across cellular membranes, altering the pharmacokinetics, and/or modulating the localization of nucleic acid molecules of the invention. The present invention encompasses the design and synthesis of novel conjugates and complexes for the delivery of molecules, including but not limited to small

molecules, lipids, phospholipids, nucleosides, nucleotides, nucleic acids, antibodies, toxins, negatively charged polymers and other polymers, for example proteins, peptides, hormones, carbohydrates, polyethylene glycols, or polyamines, across cellular membranes. In general, the transporters described are designed to be used either individually or as part of a multi-component system, with or without degradable linkers. These compounds are expected to improve delivery and/or localization of nucleic acid molecules of the invention into a number of cell types originating from different tissues, in the presence or absence of serum (see Sullenger and Cech, US 5,854,038). Conjugates of the molecules described herein can be attached to biologically active molecules via linkers that are biodegradable, such as biodegradable nucleic acid linker molecules.

The term "biodegradable nucleic acid linker molecule" as used herein, refers to a nucleic acid molecule that is designed as a biodegradable linker to connect one molecule to another molecule, for example, a biologically active molecule. The stability of the biodegradable nucleic acid linker molecule can be modulated by using various combinations of ribonucleotides, deoxyribonucleotides, and chemically modified nucleotides, for example, 2'-O-methyl, 2'-fluoro, 2'-amino, 2'-O-amino, 2'-C-allyl, 2'-O-allyl, and other 2'-modified or base modified nucleotides. The biodegradable nucleic acid linker molecule can be a dimer, trimer, tetramer or longer nucleic acid molecule, for example, an oligonucleotide of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length, or can comprise a single nucleotide with a phosphorus based linkage, for example, a phosphoramidate or phosphodiester linkage. The biodegradable nucleic acid linker molecule can also comprise nucleic acid backbone, nucleic acid sugar, or nucleic acid base modifications.

The term "biodegradable" as used herein, refers to degradation in a biological system, for example enzymatic degradation or chemical degradation.

The term "biologically active molecule" as used herein, refers to compounds or molecules that are capable of eliciting or modifying a biological response in a system. Non-limiting examples of biologically active molecules contemplated by the instant invention include therapeutically active molecules such as antibodies, hormones, antivirals, peptides, proteins, chemotherapeutics, small molecules, vitamins, co-factors, nucleosides, nucleotides, oligonucleotides, enzymatic nucleic acids, antisense nucleic acids, triplex forming oligonucleotides, 2,5-A chimeras, siRNA, dsRNA, allozymes, aptamers, decoys and analogs thereof. Biologically active molecules of the invention also include molecules capable of modulating the pharmacokinetics and/or pharmacodynamics of other biologically active

molecules, for example, lipids and polymers such as polyamines, polyamides, polyethylene glycol and other polyethers.

The term "phospholipid" as used herein, refers to a hydrophobic molecule comprising at least one phosphorus group. For example, a phospholipid can comprise a phosphorus containing group and saturated or unsaturated alkyl group, optionally substituted with OH, COOH, oxo, amine, or substituted or unsubstituted aryl groups.

Therapeutic nucleic acid molecules (*e.g.*, enzymatic nucleic acid molecules and antisense nucleic acid molecules) delivered exogenously are optimally stable within cells until translation of the target RNA has been inhibited long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. These nucleic acid molecules should be resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

In another embodiment, nucleic acid catalysts having chemical modifications that maintain or enhance enzymatic activity are provided. Such nucleic acids are also generally more resistant to nucleases than unmodified nucleic acid. Thus, in a cell and/or *in vivo* the activity of the nucleic acid may not be significantly lowered. As exemplified herein such enzymatic nucleic acids are useful in a cell and/or *in vivo* even if activity over all is reduced 10 fold (Burgin *et al.*, 1996, *Biochemistry*, 35, 14090). Such enzymatic nucleic acids herein are said to "maintain" the enzymatic activity of an all RNA ribozyme or all DNA DNAzyme.

In another aspect the nucleic acid molecules comprise a 5' and/or a 3'- cap structure.

By "cap structure" is meant chemical modifications, which have been incorporated at either terminus of the oligonucleotide (see for example Wincott *et al.*, WO 97/26270, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and can help in delivery and/or localization within a cell. The cap can be present at the 5'-terminus (5'-cap) or at the 3'-terminus (3'-cap) or can be present on both terminus. In non-limiting examples, the 5'-cap includes inverted abasic residue (moiety), 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide, 4'-thio nucleotide, carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-

dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety (for more details see Wincott *et al.*, International PCT publication No. WO 97/26270, incorporated by reference herein).

In another embodiment the 3'-cap includes, for example 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate, 3-aminopropyl phosphate; 6-aminohexyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; phosphorodithioate; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer, 1993, *Tetrahedron* 49, 1925; incorporated by reference herein).

By the term "non-nucleotide" is meant any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkyl group can be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH3)_2$, amino, or SH. The term also includes alkenyl groups which are unsaturated hydrocarbon groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons. More preferably it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group can be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, $N(CH_3)_2$, amino, or SH. The term "alkyl" also includes alkynyl groups which have an unsaturated hydrocarbon group containing at least

one carbon-carbon triple bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group can be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino or SH.

Such alkyl groups can also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group which has at least one ring having a conjugated p electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which can be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above). Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An "amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alkylaryl or hydrogen. An "ester" refers to an -C(O)-OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

By "nucleotide" is meant a heterocyclic nitrogenous base in N-glycosidic linkage with a phosphorylated sugar. Nucleotides are recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see for example, Usman and McSwiggen, supra; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, supra all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, Nucleic Acids Res. 22, 2183. Some of the non-limiting examples of chemically modified and other natural nucleic acid bases that can be introduced into nucleic acids include, for example, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (e.g.,

5-methylcytidine), 5-alkyluridines (e.g., ribothymidine), 5-halouridine (e.g., 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (e.g. 6-methyluridine), propyne, quesosine, 2-thiouridine, 4-thiouridine, wybutosine, wybutoxosine, 4-acetylcytidine, 5-(carboxyhydroxymethyl)uridine, 5'-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluridine, beta-D-galactosylqueosine, 1-methyladenosine, 1-methylinosine, 2,2-dimethylguanosine, 3-methylcytidine, 2-methyladenosine, 2-methylguanosine, N6-methyladenosine, 7-methylguanosine, 5-methoxyaminomethyl-2-thiouridine, 5-methylaminomethyluridine, 5-methylcarbonylmethyluridine, 5-methyloxyuridine, 5-methyl-2-thiouridine, 2-methylthio-N6-isopentenyladenosine, beta-D-mannosylqueosine, uridine-5-oxyacetic acid, 2-thiocytidine, threonine derivatives and others (Burgin *et al.*, 1996, Biochemistry, 35, 14090; Uhlman & Peyman, supra). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents; such bases can be used at any position, for example, within the catalytic core of an enzymatic nucleic acid molecule and/or in the substrate-binding regions of the nucleic acid molecule.

By "nucleoside" is meant a heterocyclic nitrogenous base in N-glycosidic linkage with a sugar. Nucleosides are recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleoside sugar moiety. Nucleosides generally comprise a base and sugar group. The nucleosides can be unmodified or modified at the sugar, and/or base moiety, (also referred to interchangeably as nucleoside analogs, modified nucleosides, non-natural nucleosides, non-standard nucleosides and other; see for example, Usman and McSwiggen, supra; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, supra all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, Nucleic Acids Res. 22, 2183. Some of the non-limiting examples of chemically modified and other natural nucleic acid bases that can be introduced into nucleic acids include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (e.g., 5-methylcytidine), 5-alkyluridines (e.g., ribothymidine), 5-halouridine (e.g., 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (e.g. 6-methyluridine), propyne, quesosine, 2-thiouridine, 4-thiouridine, wybutosine, wybutoxosine, 4-acetylcytidine, 5-(carboxyhydroxymethyl)uridine, 5'-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluridine, beta-D-galactosylqueosine, 1-methyladenosine, 1-methylinosine, 2,2-dimethylguanosine, 3-methylcytidine, 2-methyladenosine, 2-methylguanosine, N6-methyladenosine, 7-methylguanosine, 5-

methoxyaminomethyl-2-thiouridine, 5-methylaminomethyluridine, 5-methylcarbonylmethyluridine, 5-methyloxyuridine, 5-methyl-2-thiouridine, 2-methylthio-N6-isopentenyladenosine, beta-D-mannosylqueosine, uridine-5-oxyacetic acid, 2-thiocytidine, threonine derivatives and others (Burgin *et al.*, 1996, Biochemistry, 35, 14090; Uhlman & Peyman, supra). By "modified bases" in this aspect is meant nucleoside bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents; such bases can be used at any position, for example, within the catalytic core of an enzymatic nucleic acid molecule and/or in the substrate-binding regions of the nucleic acid molecule.

In one embodiment, the invention features modified enzymatic nucleic acid molecules with phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, morpholino, amidate carbamate, carboxymethyl, acetamidate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions. For a review of oligonucleotide backbone modifications see Hunziker and Leumann, 1995, *Nucleic Acid Analogues: Synthesis and Properties*, in *Modern Synthetic Methods*, VCH, 331-417, and Mesmaeker *et al.*, 1994, *Novel Backbone Replacements for Oligonucleotides*, in *Carbohydrate Modifications in Antisense Research*, ACS, 24-39. These references are hereby incorporated by reference herein.

By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position, for example a 3',3'-linked or 5',5'-linked deoxyabasic ribose derivative (for more details see Wincott *et al.*, International PCT publication No. WO 97/26270).

By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, thymine, uracil joined to the 1' carbon of β-D-ribo-furanose.

By "modified nucleoside" is meant any nucleotide base which contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate.

In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH_2 or 2'-*O*- NH_2, which can be modified or unmodified. Such modified groups are described, for example, in Eckstein *et al.*, U.S. Patent 5,672,695 and Matulic-Adamic *et al.*, WO 98/28317, respectively, which are both incorporated by reference in their entireties.

Various modifications to nucleic acid (*e.g.*, antisense and ribozyme) structure can be made to enhance the utility of these molecules. For example, such modifications can enhance

shelf-life, half-life *in vitro*, stability, and ease of introduction of such oligonucleotides to the target site, including, *e.g.*, enhancing penetration of cellular membranes and conferring the ability to recognize and bind to targeted cells.

Use of the nucleic acid-based molecules of the invention can lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple enzymatic nucleic acid molecules targeted to different genes, enzymatic nucleic acid molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations of enzymatic nucleic acid molecules (including different enzymatic nucleic acid molecule motifs) and/or other chemical or biological molecules). The treatment of patients with nucleic acid molecules can also include combinations of different types of nucleic acid molecules. Therapies can be devised which include a mixture of enzymatic nucleic acid molecules (including different enzymatic nucleic acid molecule motifs), allozymes, antisense, dsRNA, aptamers, and/or 2-5A chimera molecules to one or more targets to alleviate symptoms of a disease.

Administration of Nucleic Acid Molecules

Methods for the delivery of nucleic acid molecules are described in Akhtar *et al.*, 1992, *Trends Cell Bio.*, 2, 139; and *Delivery Strategies for Antisense Oligonucleotide Therapeutics*, ed. Akhtar, 1995 which are both incorporated herein by reference. Sullivan *et al.*, PCT WO 94/02595, further describes the general methods for delivery of enzymatic RNA molecules. These protocols can be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules can be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. Alternatively, the nucleic acid/vehicle combination is locally delivered by direct injection or by use of an infusion pump. Other routes of delivery include, but are not limited to oral (tablet or pill form) and/or intrathecal delivery (Gold, 1997, *Neuroscience,* 76, 1153-1158). Other approaches include the use of various transport and carrier systems, for example though the use of conjugates and biodegradable polymers. For a comprehensive review on drug delivery strategies including CNS delivery, see Ho *et al.*, 1999, *Curr. Opin. Mol. Ther.*, 1, 336-343 and Jain, *Drug Delivery Systems: Technologies and Commercial Opportunities*, Decision Resources, 1998 and Groothuis *et al.*, 1997, *J. NeuroVirol.*, 3, 387-400. More detailed descriptions of nucleic acid delivery and administration are provided in Sullivan *et al.*, supra, Draper *et al.*, PCT

WO93/23569, Beigelman *et al.*, PCT WO99/05094, and Klimuk *et al.*, PCT WO99/04819 all of which have been incorporated by reference herein.

The molecules of the instant invention can be used as pharmaceutical agents. Pharmaceutical agents prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state in a patient.

The polynucleotides of the invention can be administered (*e.g.*, RNA, DNA or protein) and introduced into a patient by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as tablets, capsules or elixirs for oral administration; suppositories for rectal administration; sterile solutions; suspensions for injectable administration; and the other compositions known in the art.

The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic administration, into a cell or patient, preferably a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell (*i.e.*, a cell to which the negatively charged polymer is desired to be delivered to). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms which prevent the composition or formulation from exerting its effect.

By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes which lead to systemic absorption include, without limitations: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes expose the desired negatively charged polymers, *e.g.*, nucleic acids, to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention can

potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation which can facilitate the association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach can provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells, such as cells implicated in endometriosis, birth control, endometrial tumors, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), menopausal dysfunction, and endometrial carcinoma.

By pharmaceutically acceptable formulation is meant, a composition or formulation that allows for the effective distribution of the nucleic acid molecules of the instant invention in the physical location most suitable for their desired activity. Non-limiting examples of agents suitable for formulation with the nucleic acid molecules of the instant invention include: PEG conjugated nucleic acids, phospholipid conjugated nucleic acids, nucleic acids containing lipophilic moieties, phosphorothioates, P-glycoprotein inhibitors (such as Pluronic P85) which can enhance entry of drugs into various tissues, for example the CNS (Jolliet-Riant and Tillement, 1999, *Fundam. Clin. Pharmacol.*, 13, 16-26); biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery after implantation (Emerich, DF *et al*, 1999, *Cell Transplant*, 8, 47-58) Alkermes, Inc. Cambridge, MA; and loaded nanoparticles, such as those made of polybutylcyanoacrylate, which can deliver drugs across the blood brain barrier and can alter neuronal uptake mechanisms (*Prog Neuropsychopharmacol Biol Psychiatry*, 23, 941-949, 1999). Other non-limiting examples of delivery strategies, including CNS delivery of the nucleic acid molecules of the instant invention include material described in Boado *et al.*, 1998, *J. Pharm. Sci.*, 87, 1308-1315; Tyler *et al.*, 1999, *FEBS Lett.*, 421, 280-284; Pardridge *et al.*, 1995, *PNAS USA.*, 92, 5592-5596; Boado, 1995, *Adv. Drug Delivery Rev.*, 15, 73-107; Aldrian-Herrada *et al.*, 1998, *Nucleic Acids Res.*, 26, 4910-4916; and Tyler *et al.*, 1999, *PNAS USA.*, 96, 7053-7058. All these references are hereby incorporated herein by reference.

The invention also features the use of the composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-circulating liposomes or stealth liposomes). Nucleic acid molecules of the invention can also comprise covalently attached PEG molecules of various molecular weights. These formulations offer a method for increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al. Chem. Rev.* 1995, 95, 2601-2627; Ishiwata *et al., Chem.*

Pharm. Bull. 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al., Science* 1995, 267, 1275-1276; Oku *et al.,* 1995, *Biochim. Biophys. Acta,* 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu *et al., J. Biol. Chem.* 1995, 42, 24864-24870; Choi *et al.,* International PCT Publication No. WO 96/10391; Ansell *et al.,* International PCT Publication No. WO 96/10390; Holland *et al.,* International PCT Publication No. WO 96/10392; all of which are incorporated by reference herein). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid accumulation in metabolically aggressive MPS tissues such as the liver and spleen. All of these references are incorporated by reference herein.

The present invention also includes compositions prepared for storage or administration which include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985) hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors which those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

The nucleic acid molecules of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or

infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a nucleic acid molecule of the invention and a pharmaceutically acceptable carrier. One or more nucleic acid molecules of the invention can be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing nucleic acid molecules of the invention can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters

derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and

isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The nucleic acid molecules of the invention can also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

It is understood that the specific dose level for any particular patient depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

The nucleic acid molecules of the present invention can also be administered to a patient in combination with other therapeutic compounds to increase the overall therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

Alternatively, certain of the nucleic acid molecules of the instant invention can be expressed within cells from eukaryotic promoters (*e.g.*, Izant and Weintraub, 1985, *Science*, 229, 345; McGarry and Lindquist, 1986, *Proc. Natl. Acad. Sci.*, USA 83, 399; Scanlon *et al.*, 1991, *Proc. Natl. Acad. Sci. USA*, 88, 10591-5; Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Dropulic *et al.*, 1992, *J. Virol.*, 66, 1432-41; Weerasinghe *et al.*, 1991, *J. Virol.*, 65, 5531-4; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. USA*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Sarver *et al.*, 1990 *Science*, 247, 1222-1225; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Good *et al.*, 1997, *Gene Therapy*, 4, 45; all of these references are hereby incorporated in their totalities by reference herein). Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a enzymatic nucleic acid (Draper *et al.*, PCT WO 93/23569, and Sullivan *et al.*, PCT WO 94/02595; Ohkawa *et al.*, 1992, *Nucleic Acids Symp. Ser.*, 27, 15-6; Taira *et al.*, 1991, *Nucleic Acids Res.*, 19, 5125-30; Ventura *et al.*, 1993, *Nucleic Acids Res.*, 21, 3249-55; Chowrira *et al.*, 1994, *J. Biol. Chem.*, 269, 25856; all of these references are hereby incorporated in their totalities by reference herein). Gene therapy approaches specific to the CNS are described by Blesch *et al.*, 2000, *Drug News Perspect.*, 13, 269-280; Peterson *et al.*, 2000, *Cent. Nerv. Syst. Dis.*, 485-508; Peel and Klein, 2000, *J. Neurosci. Methods*, 98, 95-104; Hagihara *et al.*, 2000, *Gene Ther.*, 7, 759-763; and Herrlinger *et al.*, 2000, *Methods Mol. Med.*, 35, 287-312. AAV-mediated delivery of nucleic acid to cells of the nervous system is further described by Kaplitt *et al.*, US 6,180,613.

In another aspect of the invention, RNA molecules of the present invention are preferably expressed from transcription units (see for example Couture *et al.*, 1996, *TIG.*, 12, 510) inserted into DNA or RNA vectors. The recombinant vectors are preferably DNA plasmids or viral vectors. Ribozyme expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. Preferably, the recombinant vectors capable of expressing the nucleic acid molecules are delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the nucleic acid molecule binds to the target mRNA. Delivery of nucleic acid molecule expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.*, 1996, *TIG.*, 12, 510).

In one aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the nucleic acid molecules of the instant invention. The nucleic acid sequence encoding the nucleic acid molecule of the instant invention is operably linked in a manner which allows expression of that nucleic acid molecule.

In another aspect the invention features an expression vector comprising: a) a transcription initiation region (*e.g.*, eukaryotic pol I, II or III initiation region); b) a transcription termination region (*e.g.*, eukaryotic pol I, II or III termination region); c) a nucleic acid sequence encoding at least one of the nucleic acid catalyst of the instant invention; and wherein said sequence is operably linked to said initiation region and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. The vector can optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the nucleic acid catalyst of the invention; and/or an intron (intervening sequences).

Transcription of the nucleic acid molecule sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters are expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type depends on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, *Proc. Natl. Acad. Sci. U S A*, 87, 6743-7; Gao and Huang 1993, *Nucleic Acids Res.*., 21, 2867-72; Lieber *et al.*, 1993, *Methods Enzymol.*, 217, 47-66; Zhou *et al.*, 1990, *Mol. Cell. Biol.*, 10, 4529-37). All of these references are incorporated by reference herein. Several investigators have demonstrated that nucleic acid molecules, such as ribozymes expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. U S A*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Yu *et al.*, 1993, *Proc. Natl. Acad. Sci. U S A*, 90, 6340-4; L'Huillier *et al.*, 1992, *EMBO J.*, 11, 4411-8; Lisziewicz *et al.*, 1993, *Proc. Natl. Acad. Sci. U. S. A*, 90, 8000-4; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Sullenger & Cech, 1993, *Science*, 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as ribozymes in cells (Thompson *et al.*, *supra*; Couture and Stinchcomb, *1996, supra*; Noonberg *et al.*, 1994, *Nucleic Acid Res.*, 22, 2830; Noonberg *et al.*, US Patent No. 5,624,803; Good *et al.*, 1997, *Gene Ther.*, 4, 45; Beigelman *et al.*, International PCT Publication No. *WO*

96/18736; all of these publications are incorporated by reference herein. The above ribozyme transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, *1996, supra).*

In another aspect the invention features an expression vector comprising nucleic acid sequence encoding at least one of the nucleic acid molecules of the invention, in a manner which allows expression of that nucleic acid molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; c) a nucleic acid sequence encoding at least one said nucleic acid molecule; and wherein said sequence is operably linked to said initiation region and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule.

In another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; d) a nucleic acid sequence encoding at least one said nucleic acid molecule, wherein said sequence is operably linked to the 3'-end of said open reading frame; and wherein said sequence is operably linked to said initiation region, said open reading frame and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. In yet another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) a nucleic acid sequence encoding at least one said nucleic acid molecule; and wherein said sequence is operably linked to said initiation region, said intron and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule.

In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; e) a nucleic acid sequence encoding at least one said nucleic acid molecule, wherein said sequence is operably linked to the 3'-end of said open reading frame; and wherein said sequence is operably linked to said initiation region, said intron, said open reading frame and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule.

Flt-1 (VEGFR1), KDR (VEGFR2) and/or flk-1 are attractive nucleic acid-based therapeutic targets by several criteria. The interaction between VEGF and VEGF-R is well-established. Efficacy can be tested in well-defined and predictive animal models. Finally, the disease conditions are serious and current therapies are inadequate. Whereas protein-based

therapies are designed to affect VEGF activity, nucleic acid-based therapy based on the molecules and methods described herein provides a direct and elegant approach to directly modulate flt-1, KDR and/or flk-1 expression.

Because VEGFR1 and VEGFR2 mRNAs are highly homologous in certain regions, some nucleic acid target sites are also homologous. In this case, a single nucleic acid molecule of the invention can target both VEGFR1 and VEGFR2 mRNAs. At partially homologous sites, a single nucleic acid molecule can sometimes be designed to accommodate a site on both mRNAs by including G/U base pairing. For example, if there is a G present in a enzymatic nucleic acid target site in VEGFR1 mRNA at the same position there is an A in the VEGFR2 enzymatic nucleic acid target site, the enzymatic nucleic acid can be synthesized with a U at the complementary position and it will bind both to sites. The advantage of onc enzymatic nucleic acid that targets both VEGFR1 and VEGFR2 mRNAs is clear, especially in cases where both VEGF receptors may contribute to the progression of angiogenesis in the disease state.

Examples

The following are non-limiting examples showing the selection, isolation, synthesis and activity of exemplary nucleic acids of the instant invention.

The following examples demonstrate the selection and design of antisense, aptamer, dsRNA, allozyme, hammerhead, DNAzyme, NCH, Amberzyme, Zinzyme, or G-Cleaver ribozyme molecules and binding/cleavage sites within VEGF, VEGFR1 and/or VEGFR2 RNA.

Example 1: Enzymatic nucleic acid-mediated inhibition of angiogenesis *in vivo*

The study described below was performed to assess the anti-angiogenic activity of hammerhead ribozymes targeted against flt-1 4229 site (SED ID NO: 5977) in the rat cornea model of VEGF induced angiogenesis (see above). These ribozymes have either active or inactive catalytic core and either bind and cleave or just bind to VEGF-R mRNA of the flt-1 subtype. The active ribozymes, that are able to bind and cleave the target RNA, have been shown to inhibit (^{125}I-labeled) VEGF binding in cultured endothelial cells and produce a dose-dependent decrease in VEGF induced endothelial cell proliferation in these cells. The catalytically inactive forms of these ribozymes, which can only bind to the RNA but cannot catalyze RNA cleavage, failed to inhibit VEGF binding and failed to decrease VEGF induced endothelial cell proliferation. The ribozymes and VEGF were co-delivered using the filter

disk method: Nitrocellulose filter disks (Millipore®) of 0.057 diameter were immersed in appropriate solutions and were surgically implanted in rat cornea as described by Pandey *et al., supra*. This delivery method has been shown to deliver rhodamine-labeled free ribozyme to scleral cells and, in all likelihood cells of the pericorneal vascular plexus. Since the active ribozymes show cell culture efficacy and can be delivered to the target site using the disk method, it is essential that these ribozymes be assessed for *in vivo* anti-angiogenic activity.

The stimulus for angiogenesis in this study was the treatment of the filter disk with 30 μM VEGF which is implanted within the cornea's stroma. This dose yields reproducible neovascularization stemming from the pericorneal vascular plexus growing toward the disk in a dose-response study 5 days following implant. Filter disks treated only with the vehicle for VEGF show no angiogenic response. The ribozymes were co-adminstered with VEGF on a disk in two different ribozyme concentrations. One concern with the simultaneous administration is that the ribozymes will not be able to inhibit angiogenesis since VEGF receptors can be stimulated. However, we have observed that in low VEGF doses, the neovascular response reverts to normal suggesting that the VEGF stimulus is essential for maintaining the angiogenic response. Blocking the production of VEGF receptors using simultaneous administration of anti-VEGF-R mRNA ribozymes could attenuate the normal neovascularization induced by the filter disk treated with VEGF.

<u>Materials and Methods:</u>

1. <u>Stock hammerhead ribozyme solutions:</u>

   a. flt-1 4229 (786 μM)– Active

   b. flt-1 4229 (736 μM)– Inactive

2. <u>Experimantal solutions/groups:</u>

Group 1 Solution 1 Control VEGF solution: 30 μM in 82mM Tris base

Group 2 Solution 2 flt-1 4229 (1 μg/μL) in 30 μM VEGF/82 mM Tris base

Group 3 Solution 3 flt-1 4229 (10 μg/μL) in 30 μM VEGF/82 mM Tris base

Group 4 Solution 4 No VEGF, flt-1 4229 (10 μg/μL) in 82 mM Tris base

Group 5 Solution 5 No VEGF, No ribozyme in 82 mM Tris base

10 eyes per group, 5 animals (Since they have similar molecular weights, the molar concentrations should be essentially similar).

Each solution (VEGF and RIBOZYMES) were prepared as a 2X solution for 1:1 mixing for final concentrations above, with the exception of solution 1 in which VEGF was 2X and diluted with ribozyme diluent (sterile water).

3. VEGF Solutions

The 2X VEGF solution (60 μM) was prepared from a stock of 0.82 μg/μL in 50 mM Tris base. 200 μL of VEGF stock was concentrated by speed vac to a final volume of 60.8 μL, for a final concentration of 2.7 μg/μL or 60 μM. Six 10 μL aliquots was prepared for daily mixing. 2X solutions for VEGF and Ribozyme was stored at 4°C until the day of the surgery. Solutions were mixed for each day of surgery. Original 2X solutions was prepared on the day before the first day of the surgery.

4. Surgical Solutions:

Anesthesia:

stock ketamine hydrochloride 100 mg/mL

stock xylazine hydrochloride 20 mg/mL

stock acepromazine 10 mg/mL

Final anesthesia solution: 50 mg/mL ketamine, 10 mg/mL xylazine, and 0.5 mg/mL acepromazine

5% povidone iodine for opthalmic surgical wash

2% lidocaine (sterile) for opthalmic administration (2 drops per eye)

sterile 0.9% NaCl for opthalmic irrigation

5. Surgical Methods:

Standard surgical procedure as described in Pandey *et al., supra*. Filter disks were incubated in 1 μL of each solution for approximately 30 minutes prior to implantation.

6. Experimental Protocol:

The animal cornea were treated with the treatment groups as described above. Animals were allowed to recover for 5 days after treatment with daily observation (scoring 0 - 3). On the fifth day animals were euthanized and digital images of each eye was obtained for quantitaion using Image Pro Plus. Quantitated neovascular surface area were analyzed by ANOVA followed by two post-hoc tests including Dunnets and Tukey-Kramer tests for significance at the 95% confidence level. Dunnets provide information on the significance between the differences within the means of treatments vs. controls while Tukey-Kramer provide information on the significance of differences within the means of each group.

The flt-1 4229 (SEQ ID NO: 5977) active hammerhead ribozyme at both concentrations was effective at inhibiting angiogenesis while the inactive ribozyme did not show any significant reduction in angiogenesis. A statistically signifiant reduction in neovascular surface area was observed only with active ribozymes. This result clearly shows that the ribozymes are capable of significantly inhibiting angiogenesis *in vivo*. Specifically, given ribozyme mechanism of action, the observed inhibition is by the binding and cleavage of target RNA by ribozymes.

Example 2: Bioactivity of anti-angiogenesis ribozymes targeting *flt-1* and *kdr* RNA

MATERIALS AND METHODS

Ribozymes : Hammerhead ribozymes and controls designed to have attenuated activity (attenuated controls) were synthesized and purified as previously described above. The attenuated ribozyme controls maintain the binding arm sequence of the parent ribozyme and thus are still capable of binding to the mRNA target. However, they have two nucleotide changes in the core sequence that substantially reduce their ability to carry out the cleavage reaction. Ribozymes were designed to target *Flt-1* or *KDR* mRNA sites conserved in human, mouse, and rat. In general, ribozymes with binding arms of seven nucleotides were designed and tested. If, however, only six nucleotides surrounding the cleavage site were conserved in all three species, six nucleotide binding arms were used. Data are presented herein for 2'-NH_2 uridine modified ribozymes in cell proliferation studies and for 2'-*C*-allyl uridine modified ribozymes in RNAse protection, *in vitro* cleavage and corneal studies.

***In vitro* ribozyme cleavage assays:** *In vitro* RNA cleavage rates on a 15 nucleotide synthetic RNA substrate were measured as previously described above.

Cell culture: Human dermal microvascular endothelial cells (HMVEC-d, Clonetics Corp.) were maintained at 37°C in flasks or plates coated with 1.5% porcine skin gelatin (300

bloom, Sigma) in Growth medium (Clonetics Corp.) supplemented with 10-20% fetal bovine serum (FBS, Hyclone). Cells were grown to confluency and used up to the seventh passage. Stimulation medium consisted of 50% Sigma 99 media and 50% RPMI 1640 with L-glutamine and additional supplementation with 10 μg/mL Insulin-Transferrin-Selenium (Gibco BRL) and 10% FBS. Cell growth was stimulated by incubation in Stimulation medium supplemented with 20 ng/mL of either $VEGF_{165}$ or bFGF. $VEGF_{165}$ (165 amino acids) was selected for cell culture and animal studies because it is the predominant form of the four native forms of VEGF generated by alternative mRNA splicing. Cell culture assays were carried out in triplicate.

Ribozyme and ribozyme/LIPOFECTAMINE™ formulations:

Cell culture: Ribozymes or attenuated controls (50-200 nM) were formulated for cell culture studies and used immediately. Formulations were carried out with LIPOFECTAMINE™ (Gibco BRL) at a 3:1 lipid to phosphate charge ratio in serum-free medium (OPTI-MEM™, Gibco BRL) by mixing for 20 minutes at room temperature. For example, a 3:1 lipid to phosphate charge ratio was established by complexing 200 nM ribozyme with 10.8 μg/μL LIPOFECTAMINE™ (13.5 μM DOSPA).

In vivo: For corneal studies, lyophilized ribozyme or attenuated controls were resuspended in sterile water at a final stock concentration of 170 μg/μL (highest dose). Lower doses (1.7-50 μg/μL) were prepared by serial dilution in sterile water.

Proliferation assay: HMVEC-d were seeded (5×10^3 cells/well) in 48-well plates (Costar) and incubated 24-30 hours in Growth medium at 37°C. After removal of the Growth medium, cells were treated with 50-200 nM LIPOFECTAMINE™ complexes of ribozyme or attenuated controls for 2 hours in OPTI-MEM™. The ribozyme/control-containing medium was removed and the cells were washed extensively in 1X PBS. The medium was then replaced with Stimulation medium or Stimulation medium supplemented with 20 ng/mL $VEGF_{165}$ or bFGF. After 48 hours, the cell number was determined using a Coulter™ cell counter. Data are presented as cell number per well following 48 hours of VEGF stimulation.

RNAse protection assay: HMVEC-d were seeded (2×10^5 cells/well) in 6-well plates (Costar) and allowed to grow 32-36 hours in Growth medium at 37°C. Cells were treated with LIPOFECTAMINE™ complexes containing 200 nM ribozyme or attenuated control for 2 h as described under "Proliferation Assay" and then incubated in Growth medium containing 20 ng/mL $VEGF_{165}$ for 24 hours. Cells were harvested and an RNAse protection assay was carried out using the Ambion Direct Protect kit and protocol with the exception that 50 mM

EDTA was added to the lysis buffer to eliminate the possibility of ribozyme cleavage during sample preparation. Antisense RNA probes targeting portions of *Flt-1* and *KDR* were prepared by transcription in the presence of [^{32}P]-UTP. Samples were analyzed on polyacrylamide gels and the level of protected RNA fragments was quantified using a Molecular Dynamics PhosphorImager. The levels of *Flt-1* and *KDR* were normalized to the level of cyclophilin (human cyclophilin probe template, Ambion) in each sample. The coefficient of variation for cyclophilin levels was 11% [265940 cpm ± 29386 (SD)] for all conditions tested here (*i.e.* in the presence of either active ribozymes or attenuated controls). Thus, cyclophilin is useful as an internal standard in these studies.

Rat corneal pocket assay of VEGF-induced angiogenesis:

Animal guidelines and anesthesia. Animal housing and experimentation adhered to standards outlined in the 1996 Guide for the Care and Use of Laboratory Animals (National Research Council). Male Sprague Dawley rats (250-300 g) were anesthetized with ketamine (50 mg/kg), xylazine (10 mg/kg), and acepromazine (0.5 mg/kg) administered intramuscularly (im). The level of anesthesia was monitored every 2-3 min by applying hind limb paw pressure and examining for limb withdrawal. Atropine (0.4 mg/kg, im) was also administered to prevent potential corneal reflex-induced bradycardia.

Preparation of VEGF soaked disk. For corneal implantation, 0.57 mm diameter nitrocellulose disks, prepared from 0.45 μm pore diameter nitrocellulose filter membranes (Millipore Corporation), were soaked for 30 min in 1 μL of 30 μM $VEGF_{165}$ in 82 mM Tris·HCl (pH 6.9) in covered petri dishes on ice.

Corneal surgery. The rat corneal model used in this study was a modified from Koch *et al. Supra* and Pandey *et al., supra*. Briefly, corneas were irrigated with 0.5% povidone iodine solution followed by normal saline and two drops of 2% lidocaine. Under a dissecting microscope (Leica MZ-6), a stromal pocket was created and a presoaked filter disk (see above) was inserted into the pocket such that its edge was 1 mm from the corneal limbus.

Intraconjunctival injection of test solutions. Immediately after disk insertion, the tip of a 40-50 μm OD injector (constructed in our laboratory) was inserted within the conjunctival tissue 1 mm away from the edge of the corneal limbus that was directly adjacent to the VEGF-soaked filter disk. Six hundred nanoliters of test solution (ribozyme, attenuated control or sterile water vehicle) were dispensed at a rate of 1.2 μL/min using a syringe pump (Kd Scientific). The injector was then removed, serially rinsed in 70% ethanol and sterile water and immersed in sterile water between each injection. Once the test solution was injected,

closure of the eyelid was maintained using microaneurism clips until the animal began to recover gross motor activity. Following treatment, animals were warmed on a heating pad at 37°C.

Animal treatment groups/experimental protocol. Ribozymes targeting *Flt-1* site 4229 (SEQ ID NO: 5977) and *KDR* mRNA site 726 (SEQ ID NO: 5978) were tested in the corneal model along with their attenuated controls. Five treatment groups were assigned to examine the effects of five doses of each test substance over a dose range of 1-100 µg on VEGF-stimulated angiogenesis. Negative (30 µM VEGF soaked filter disk and intraconjunctival injection of 600 nL sterile water) and no stimulus (Tris-soaked filter disk and intraconjunctival injection of sterile water) control groups were also included. Each group consisted of five animals (10 eyes) receiving the same treatment.

Quantitation of angiogenic response. Five days after disk implantation, animals were euthanized following im administration of 0.4 mg/kg atropine and corneas were digitally imaged. The neovascular surface area (NSA, expressed in pixels) was measured *postmortem* from blood-filled corneal vessels using computerized morphometry (Image Pro Plus, Media Cybernetics, v2.0). The individual mean NSA was determined in triplicate from three regions of identical size in the area of maximal neovascularization between the filter disk and the limbus. The number of pixels corresponding to the blood-filled corneal vessels in these regions was summated to produce an index of NSA. A group mean NSA was then calculated. Data from each treatment group were normalized to VEGF/ribozyme vehicle-treated control NSA and finally expressed as percent inhibition of VEGF-induced angiogenesis.

Statistics. After determining the normality of treatment group means, group mean percent inhibition of VEGF-induced angiogenesis was subjected to a one-way analysis of variance. This was followed by two post-hoc tests for significance including Dunnett's (comparison to VEGF control) and Tukey-Kramer (all other group mean comparisons) at alpha = 0.05. Statistical analyses were performed using JMP v.3.1.6 (SAS Institute).

RESULTS

Ribozyme-mediated reduction of VEGF-induced cell proliferation: Ribozyme cleavage of *Flt-1* or *KDR* mRNA should result in a decrease in the density of cell surface VEGF receptors. This decrease should limit VEGF binding and consequently interfere with the mitogenic signaling induced by VEGF. To determine if cell proliferation was impacted by anti-*Flt-1* and/or anti-*KDR* ribozyme treatment, proliferation assays using cultured human microvascular cells were carried out. Ribozymes included in the proliferation assays were

initially chosen by their ability to decrease the level of VEGF binding to treated cells. In these initial studies, ribozymes targeting 20 sites in the coding region of each mRNA were screened. The most effective ribozymes against two sites in each target, *Flt-1* sites 1358 and 4229 and *KDR* sites 726 and 3950, were included in the proliferation assays reported here. In addition, attenuated analogs of each ribozyme were used as controls. These attenuated controls are still capable of binding to the mRNA target since the binding arm sequence is maintained. However, these controls have two nucleotide changes in the core sequence that substantially reduce their ability to carry out the cleavage reaction.

The active ribozymes tested decreased the relative proliferation of HMVEC-d after VEGF stimulation, an effect that increased with ribozyme concentration. This concentration dependency was not observed following treatment with the attenuated controls designed for these sites. In fact, little or no change in cell growth was noted following treatment with the attenuated controls, even though these controls can still bind to the specific target sequences. At 200 nM, there was a distinct "window" between the anti-proliferative effects of each ribozyme and its attenuated control; a trend also observed at lower doses. This window of inhibition of proliferation (56-77% based on total cells/well) reflects the contribution of ribozyme-mediated activity. In comparison, no effect of anti-*Flt-1* or anti-*KDR* ribozymes was noted on bFGF-stimulated cell proliferation. Moreover, an irrelevant, but active, ribozyme whose binding sequence is not found in either *Flt-1* or *KDR* mRNA had no effect in this assay. These data are consistent with the basic ribozyme mechanism in which binding and cleavage are necessary components. Although the relative surface distribution of Flt-1 and KDR receptors in this cell type is not known, the antiproliferative effects of these ribozymes indicate that, at least in cell culture, both receptors are functionally coupled to proliferation.

Specific reduction of *Flt-1* or *KDR* mRNA by ribozyme treatment: To confirm that anti-*Flt-1* and anti-*KDR* ribozymes reduce their respective mRNA targets, cellular levels of *Flt-1* or *KDR* were quantified using an RNAse protection assay with specific *Flt-1* or *KDR* probes. For each target, one ribozyme/attenuated control pair was chosen for continued study. Exposure of HMVEC-d to active ribozyme targeting *Flt-1* site 4229 decreased *Flt-1* mRNA, but not *KDR* mRNA. Likewise, treatment with the active ribozyme targeting *KDR* site 726 decreased *KDR*, but not *Flt-1* mRNA. Both ribozymes decreased the level of their respective target RNA by greater than 50%. The degree of reduction associated with the corresponding attenuated controls was not greater than 13%.

***In vitro* activity of anti-*Flt* and anti-*KDR* ribozymes.**

To confirm further the necessity of an active ribozyme core, *in vitro* cleavage activities were determined for the *Flt-1* site 4229 ribozyme and the KDR site 726 ribozyme as well as their paired attenuated controls. The first order rate constants calculated from the time-course of short substrate cleavage for the anti-*Flt-1* ribozyme and its attenuated control were $0.081 \pm 0.0007\ min^{-1}$ and $0.001 \pm 6 \times 10^{-5}\ min^{-1}$, respectively. For the anti-*KDR* ribozyme and its paired control, the first order rate constants were $0.434 \pm 0.024\ min^{-1}$ and $0.002 \pm 1 \times 10^{-4}\ min^{-1}$, respectively. Although the attenuated controls retain a very slight level of cleavage activity under these optimized conditions, the decrease in *in vitro* cleavage activity between each active ribozyme and its paired attenuated control is about two orders of magnitude. Thus, an active core is essential for cleavage activity *in vitro* and is also necessary for ribozyme activity in cell culture.

Ribozyme-mediated reduction of VEGF-induced angiogenesis *in vivo*. To assess whether ribozymes targeting VEGF receptor mRNA could impact the complex process of angiogenesis, prototypic anti-*Flt-1* and *KDR* ribozymes that were identified in cell culture studies were screened in a rat corneal pocket assay of VEGF-induced angiogenesis. In this assay, corneas implanted with VEGF-containing filter disks exhibited a robust neovascular response in the corneal region between the disk and the corneal limbus (from which the new vessels emerge). Disks containing a vehicle solution elicited no angiogenic response. In separate studies, intraconjunctival injections of sterile water vehicle did not affect the magnitude of the VEGF-induced angiogenic response. In addition, ribozyme injections alone did not induce angiogenesis.

The dose-related effects of anti-*Flt-1* or *KDR* ribozymes on the VEGF-induced angiogenic response were then examined. The antiangiogenic effect of the anti-*Flt-1* (site 4229) and *KDR* (site 726) ribozymes and their attenuated controls over a dose range from 1 to 100 μg, respectively was determined. For both ribozymes, the maximal antiangiogenic response (48 and 36% for anti-*Flt-1* and *KDR* ribozymes, respectively) was observed at a dose of 10 μg.

The anti-*Flt-1* ribozyme produced a significantly greater antiangiogenic response than its attenuated control at 3 and 10 μg ($p<0.05$). Its attenuated control exhibited a small but significant antiangiogenic response at doses above 10 μg compared to vehicle treated VEGF controls ($p<0.05$). At its maximum, this response was not significantly greater than that observed with the lowest dose of active anti-*Flt-1* ribozyme. The anti-*KDR* ribozyme significantly inhibited angiogenesis from 3 to 30 μg ($p<0.05$). The anti-*KDR* attenuated control had no significant effect at any dose tested.

Example 3. *In vivo* inhibition of tumor growth and metastases by VEGF-R ribozymes.

A. **Lewis Lung Carcinoma Mouse Model:** Ribozymes were chemically synthesized as described above. The sequence of ANGIOZYME™ bound to its target RNA is shown in **Figure 1**.

The tumors in this study were derived from a cell line (LLC-HM) which gives rise to reproducible numbers of spontaneous lung metastases when propagated *in vivo*. The LLC-HM line was obtained from Dr. Michael O'Reilly, Harvard University. Tumor neovascularization in Lewis lung carcinoma has been shown to be VEGF-dependent. Tumors from mice bearing LLC-HM (selected for the highly metastatic phenotype by serial propagation) were harvested 20 days post-inoculation. A tumor brei suspension was prepared from these tumors according to standard protocols. On day 0 of the study, 0.5×10^6 viable LLC-HM tumor cells were injected subcutaneously (sc) into the dorsum or flank of previously untreated mice (100 µL injectate). Tumors were allowed to grow for a period of 3 days prior to initiating continuous intravenous administration of saline or 30 mg/kg/d ANGIOZYME™ *via* Alzet mini-pumps. One set of animals was dosed from days 3 to 17, inclusive. Tumor length and width measurements and volumes were calculated according to the formula: Volume = $0.5(\text{length})(\text{width})^2$. At post-inoculation day 25, animals were euthanized and lungs harvested. The number of lung macrometastatic nodules was counted. It should be noted that metastatic foci were quantified 8 days after the cessation of dosing. Ribozyme solutions were prepared to deliver to another set of animals 100, 10, 3, or 1 mg/kg/day of ANGIOZYME™ *via* Alzet mini-pumps. A total of 10 animals per dose or saline control group were surgically implanted on the left flank with osmotic mini-pumps pre-filled with the respective test solution three days following tumor inoculation. Pumps were attached to indwelling jugular vein catheters.

Figure 2 shows the antitumor effects of ANGIOZYME™. There is a statistically significant inhibition ($p < 0.05$) of primary LLC-HM tumor growth in tumors grown in the flank regions compared to saline control. ANGIOZYME™ significantly reduced ($p < 0.05$) the number of lung metastatic foci in animals inoculated either in the flank regions. **Figure 3** illustrates the dose-dependent anti-metastatic effect of ANGIOZYME™ compared to saline control.

B. Mouse Colorectal Cancer Model. KM12L4a-16 is a human colorectal cancer cell line. On day 0 of the study, 0.5×10^6 KM12L4a-16 cells were implanted into the spleen of nude mice. Three days after tumor inoculation, Alzet minipumps were implanted and continuous subcutaneous delivery of either saline or 12, 36 or 100 mg/kg/ day of

ANGIOZYME™ was initiated. On day 5, the spleens containing the primary tumors were removed. On day 18, the Alzet minipumps were replaced with fresh pumps so that delivery of saline or ANGIOZYME™ was continuous over a 28 day period from day 3 to day 32. Animals were euthanized on day 41 and the liver tumor burden was evaluated.

Following treatment with 100 mg/kg/day of ANGIOZYME™, there was a significant reduction in the incidence and median number of liver metastasis (**Figure 4**). In saline-treated animals, the median number of metastases was 101. However, at the high dose of ANGIOZYME™ (100 mg/kg/day), the median number of metastases was zero.

Example 4: Effect of ANGIOZYME™ alone or in combination with chemotherapeutic agents in the mouse Lewis Lung Carcinoma Model.

Methods

Tumor inoculations. Male C57/BL6 mice, age 6 to 8 weeks, were inoculated subcutaneously in the flank with 5 x 10^5 LLC-HM cells from brei preparations made from tumors grown in mice.

Ribozymes and controls. RPI.4610, also known as ANGIOZYME™ (SEQ ID NO: 5977), is an anti-*Flt-1* ribozyme that targets site 4229 in the human *Flt-1* receptor mRNA (EMBL accession no. X51602). The controls tested include RPI.13141, an attenuated version of RPI.4610 in which four nucleotides in the catalytic core are changed so that the cleavage activity is dramatically decreased. RPI.13141, however, maintains the base composition and binding arms of RPI.4610 and so is still capable of binding to the target site. The second control (RPI.13030) also has changes to the catalytic core (three) to inhibit cleavage activity, but in addition the sequence of the binding arms has been scrambled so that it can no longer bind to the target sequence. One nucleotide in the arm of RPI.13030 is also changed to maintain the same base composition as RPI.4610.

Ribozyme administrations. Ribozymes and controls were resuspended in normal saline. Administration was initiated seven days following tumor inoculation. Animals either received a daily subcutaneous injection (30 mg/kg test substance) from day 7 to day 20 or were instrumented with an Alzet osmotic minipump (12 µL/day flow rate) containing a solution of ribozyme or control. Subcutaneous infusion pumps delivered the test substances (30 mg/kg/day) from day 7 to 20 (14-day pumps, 420 mg/kg total test substance) or days 7-34 (28-day pumps, 840 mg/kg total test substance). Where indicated, chemotherapeutic agents were given in combination with ribozyme treatment. Cyclophosphamide was given by intraperitoneal administration on days 7, 9 and 11 (125 mg/kg). Gemcitabine was given by

intraperitoneal administration on days 8, 11 and 14 (125 mg/kg). Untreated, uninstrumented animals were used as comparison. Five animals were included in each group.

Results

The antiangiogenic ribozyme, ANGIOZYME™, was tested in a model of Lewis lung carcinoma alone and in combination with two chemotherapeutic agents. Previously (see above), 30 mg/kg/day ANGIOZYME™ alone was determined to inhibit both primary tumor growth and lung metastases in a highly metastatic variant of Lewis lung (continuous 14-day iv delivery*via* Alzet minipump, manuscript in preparation).

In this study, 30 mg/kg/day ANGIOZYME™ delivered either as a daily subcutaneous bolus injection or as a continuous infusion from an Alzet minipump resulted in a delay in tumor growth. On average, tumor growth to 500 mm^3 was delayed by ~7 days in animals being treated with ANGIOZYME™ compared to an untreated group. Growth of tumors in animals being treated with either of two attenuated controls was delayed by only ~ 2 days.

ANGIOZYME™ delivered by subcutaneous bolus was also tested in combination with either Gemcytabine or cyclophosphamide. Tumor growth delay increased by about 3 days in the presence of combination therapy with ANGIOZYME™ and Gemcytabine over the effects of either treatment alone. The combination of ANGIOZYME™ and cyclophosphamide did not increase tumor growth delay over that of cyclophosphamide alone, however, suboptimal doses of cyclophosphamide were not included in this study. Neither of the attenuated controls increased the effect of the chemotherapeutic agents.

The effect of ANGIOZYME™ on metastases to the lung was also determined in the presence and absence of additional chemotherapeutic treatment. Macrometastases to the lungs were counted in two animals in each treatment group on day 20. In the presence of ANGIOZYME™, with or without a chemotherapeutic agent, the lung metastases were reduced to zero. Treatment with either Gemcytabine or cyclophosphamide alone (mean number of metastases 4.5 and 4, respectively) were not as effective as ANGIOZYME™ alone or when used in combination with ANGIOZYME™. Neither of the attenuated controls increased the effect of the chemotherapeutic agents.

The effect on metastases to the lung was also determined following continuous treatment with ANGIOZYME™. At day 20, an average of ~8 macrometastases were noted in the treatment groups which had been instrumented with Alzet minipumps (either 14- or 28-day pumps). This is a decrease in metastases of ~50% from the untreated group. Since

ANGIOZYME™ delivered by a daily subcutaneous bolus resulted in zero metastases (Fig.4) in the two animals counted, it is possible that the additional burden of being instrumented with the minipump contributes to a slightly decreased response to ANGIOZYME™.

Example 5: Identification of Potential Target Sites in Human VEGFR1 and/or VEGFR2 RNA

The sequence of human VEGFR1 and/or VEGFR2 genes are screened for accessible sites using a computer-folding algorithm. Regions of the RNA that do not form secondary folding structures and contain potential enzymatic nucleic acid molecule and/or antisense binding/cleavage sites are identified. An exemplary sequence of an enzymatic nucleic acid molecule of the invention is shown in Formula I and/or Formula II (SEQ ID Nos: 5977 and 5978, respectively). Other nucleic acid molecules and targets contemplated by the invention are described in Pavco *et al.*, US Patent Application No. 09/870,161, incorporated by reference herein in its entirety. Similarly, other nucleic acid molecules of the invention, including antisense, aptamers, dsRNA, siRNA, and/or 2,5-A chimeras, can be designed to modulate the expression of the nucleic acid targets described in Pavco *et al.,* US Patent Application No. 09/870,161.

Example 6: Selection of Enzymatic Nucleic Acid Cleavage Sites in Human VEGFR1 and/or VEGFR2 RNA

Enzymatic nucleic acid molecule target sites are chosen by analyzing sequences of human VEGFR1 receptor (for example Genbank Accession No. NM_002019), and VEGFR2 receptor (for example Genbank Accession No. NM_002253) genes and prioritizing the sites on the basis of folding. Enzymatic nucleic acid molecules are designed that can bind each target and are individually analyzed by computer folding (Christoffersen *et al.,* 1994 *J. Mol. Struc. Theochem,* 311, 273; Jaeger *et al.,* 1989, *Proc. Natl. Acad. Sci. USA*, 86, 7706) to assess whether the enzymatic nucleic acid molecule sequences fold into the appropriate secondary structure. Those enzymatic nucleic acid molecules with unfavorable intramolecular interactions between the binding arms and the catalytic core can be eliminated from consideration. As discussed herein, varying binding arm lengths can be chosen to optimize activity. Generally, at least 4 bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Example 7: Chemical Synthesis and Purification of Ribozymes and Antisense for Efficient Cleavage and/or blocking of VEGFR1 and/or VEGFR2 RNA

Enzymatic nucleic acid molecules and antisense constructs are designed to anneal to various sites in the RNA message. The binding arms of the enzymatic nucleic acid molecules are complementary to the target site sequences described above, while the antisense constructs are fully complementary to the target site sequences described above. RNAi molecules (dsRNA) likewise have one strand of RNA or a portion of RNA complementarity to the target site sequence or a portion of the target site sequence. For example, complementarity within the double-strand RNAi structure is formed from two separate individual RNA strands or from self-complementary areas of a topologically closed, individual RNA strand which can be optionally circular. The nucleic acid molecules were chemically synthesized. The method of synthesis used followed the procedure for normal RNA synthesis as described above and in Usman *et al.*, (1987 J. Am. Chem. Soc., 109, 7845), Scaringe *et al.*, (1990 Nucleic Acids Res., 18, 5433) and Wincott *et al.*, supra, and made use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. The average stepwise coupling yields were typically $\geq$98%.

Nucleic acid molecules are also synthesized from DNA templates using bacteriophage T7 RNA polymerase (Milligan and Uhlenbeck, 1989, Methods Enzymol. 180, 51). Nucleic acid molecules of the invention are purified by gel electrophoresis using general methods or are purified by high pressure liquid chromatography (HPLC; See Wincott *et al.*, supra; the totality of which is hereby incorporated herein by reference) and are resuspended in water. Examples of sequences of chemically synthesized enzymatic nucleic acid molecules are shown in Formula I (SEQ ID NO: 5977), Formula II (SEQ ID NO: 5978) and in Pavco *et al.*, US Patent Application No. 09/870,161.

Example 8: Enzymatic Nucleic Acid Molecule Cleavage of VEGFR1 and/or VEGFR2 RNA Target *in vitro*

Enzymatic nucleic acid molecules targeted to the human VEGFR1 and/or VEGFR2 RNA are designed and synthesized as described above. These enzymatic nucleic acid molecules can be tested for cleavage activity *in vitro*, for example, using the following procedure. The target sequences and the nucleotide location within the VEGFR1 and/or VEGFR2 RNA are described in Pavco *et al.*, US Patent Application No. 09/870,161.

Cleavage Reactions: Full-length or partially full-length, internally-labeled target RNA for enzymatic nucleic acid molecule cleavage assay is prepared by *in vitro* transcription in the presence of [a-^{32}P] CTP, passed over a G 50 Sephadex column by spin chromatography and used as substrate RNA without further purification. Alternately, substrates are 5'-^{32}P-end

labeled using T4 polynucleotide kinase enzyme. Assays are performed by pre-warming a 2X concentration of purified enzymatic nucleic acid molecule in enzymatic nucleic acid molecule cleavage buffer (50 mM Tris-HCl, pH 7.5 at 37°C, 10 mM $MgCl_2$) and the cleavage reaction was initiated by adding the 2X enzymatic nucleic acid molecule mix to an equal volume of substrate RNA (maximum of 1-5 nM) that was also pre-warmed in cleavage buffer. As an initial screen, assays are carried out for 1 hour at 37°C using a final concentration of either 40 nM or 1 mM enzymatic nucleic acid molecule, *i.e.*, enzymatic nucleic acid molecule excess. The reaction is quenched by the addition of an equal volume of 95% formamide, 20 mM EDTA, 0.05% bromophenol blue and 0.05% xylene cyanol after which the sample is heated to 95°C for 2 minutes, quick chilled and loaded onto a denaturing polyacrylamide gel. Substrate RNA and the specific RNA cleavage products generated by enzymatic nucleic acid molecule cleavage are visualized on an autoradiograph of the gel. The percentage of cleavage is determined by Phosphor Imager® quantitation of bands representing the intact substrate and the cleavage products.

<u>Example 9: Phase I/II Study of Repetitive Dosing of ANGIOZYME™ Targeting the VEGFR1 (FLT-1) Receptor of VEGF</u>

A ribozyme therapeutic agent ANGIOZYME™ (SEQ ID NO: 5977), was assessed by daily subcutaneous administration in a phase I/II trial for 31 patients with refractory solid tumors. Demographic information relating to patients enrolled in the study are shown in **Table III**. The primary study endpoint was to determine the safety and maximum tolerated dose of ANGIOZYME™. Secondary endpoints assessed ANGIOZYME™ pharmacokinetics and clinical response. Patients were treated at the following doses: 3 patients received doses of 10 mg/m^2/day, 4 patients received 30 mg/m^2/day, 20 patients received 100 mg/m^2/day, and 4 patients received 300 mg/m^2/day. All but one patient were dosed for a minimum of 29 consecutive days with 24-hour pharmacokinetic analyses on Day 1 and 29. Clinical response was assessed monthly. <u>Results</u> The data from 20 patients indicated that ANGIOZYME™ was well tolerated, with no systemic adverse events. **Figure 5** shows the plasma concentration profile of ANGIOZYME™ after a single subcutaneous dose of 10, 30, 100, or 300 mg/m^2. The pharmacokinetic parameters of ANGIOZYME™ after subcutaneous bolus administration are outlined in **Table IV**. An MTD (maximum tolerated dose) could not be established. One patient in the 300 mg/m^2/d group experienced a grade 3 injection site reaction. Patients in the other groups experienced intermittent grade 1 and grade 2 injection site reactions with erythema and induration. No systemic or laboratory toxicities were observed. Pharmacokinetic analyses demonstrated dose-dependent plasma concentrations with good bioavailability (70-90%), t1/2 = 209-384 min, and no accumulation after repeated

doses. To date, 17/28 (61%) of evaluable patients have had stable disease for periods of one to six months and two patients (nasopharyngeal squamous cell carcinoma and melanoma) had minor clinical responses. The patient with nasopharyngeal carcinoma demonstrated central tumor necrosis as indicated by MRI. The longest period of treatment thus far has been 8 months for two patients at 100 $mg/m^2/d$ (breast, peritoneal mesothelioma).

Example 10: Down-regulation of VEGFR1 gene expression to treat gynecologic neovascularization dependent conditions

One patient in the Phase I/II trial described in Example 19 was menstruating prior to enrollment in the ANGIOZYME™ monotherapy trial. After 1-2 months on trial, the patient's menstrual cycles ceased. The patient remained on trial for approximately 11 months and did not menstruate. The patient then went off the trial for about 4 months and the menstrual cycles resumed. Re-enrollment in the ANGIOZYME™ trial resulted in the patient's menstrual cycle stopping again. This clinical observation suggests that ANGIOZYME™ is interfering with the patient's menstrual cycle, perhaps by inhibiting neovascularization of uterine tissue. This data also suggests that ANGIOZYME™ has a direct effect on the endometrial tissue or an effect on LH/FSH stimulation. These results suggest the treatment or control, using ANGIOZYME™ (SEQ ID NO: 5977) and/or other nucleic acid molecules of the instant invention, of various clinical targets and/or processes associated with female reproduction and gynecologic neovascularization, such as endometriosis, birth control, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), menopausal dysfunction, endometrial carcinoma or other condition associated with the expression of VEGFR1 and/or VEGFR2 VEGF receptors.

Example 11: Down-regulation of VEGFR1 in clinical setting

Twenty-seven of the patients enrolled in the Phase I/II trial described in Example 19 had day 1 (baseline) and day 43 (six-week) serum samples assayed for VEGFR1 biomarker. VEGFR1 levels were statistically different after six weeks of ANGIOZYME treatment (**Figure 9**). Although statistical testing involving all 27 patients showed statistical support for effects, not all patients presented with elevated levels of VEGF-R1. Since the effects of ANGIOZYME on VEGF-R1 may only be demonstrated when sufficient levels are present at baseline, a cutoff of 100 pg/mL was chosen and changes in this VEGF-R1 were re-analyzed. Ten of the 27 patients presented with baseline VEGF-R1 levels in excess of 100 pg/mL. For this subgroup VEGF-R1 levels were lower by 3-fold, $p<.001$. After six weeks of treatment the average (geometric mean) of VEGF-R1 decreased for this subgroup from 419 pg/ml to

132pg/ml, p<.001. These results show that treatment with ANGIOZYME results in a statistically significant reduction in VEGFR1 expression.

Example 22: *In vivo* inhibition of neovascularization in an ocular animal model by VEGF-R ribozymes.

Summary of the Mouse Model: A mouse model of proliferative retinopathy (Aiello et al., 1995, *Proc. Natl. Acad. Sci. USA* 92: 10457-10461; Robinson *et al., 1996, Proc. Natl. Acad. Sci. USA* 93: 4851-4856; Pierce et al., 1996, *Archives of Ophthalmology* 114: 1219-1228) in which neovascularization of the mouse retina is induced by exposure of 7-day old mice to 75% oxygen followed by a return to normal room air. The initial period in high oxygen causes an obliteration of developing blood vessels in the retina. Exposure to room air five days later is perceived as hypoxia by the now underperfused retina. The result is an immediate upregulation of VEGF mRNA and VEGF protein (between 6-12 hours) followed by an extensive retinal neovascularization that peaks in ~5 days. Although this model is more representative of retinopathy of prematurity than diabetic retinopathy, it is an accepted small animal model in which to study neovascular pathophysiology of the retina. In fact, intravitreal injection of certain antisense DNA constructs targeting VEGF mRNA have been found to be antiangiogenic in this model, as were soluble VEGF receptor chimeric proteins designed to bind VEGF in the vitreous humor (Aiello et al., 1995, *Proc. Natl. Acad. Sci. USA* 92: 10457-10461; Robinson *et al., 1996, Proc. Natl. Acad. Sci. USA* 93: 4851-4856; Pierce et al., 1996, *Archives of Ophthalmology* 114: 1219-1228).

Summary of experiment: The effect of an anti-*KDR/Flk-1* ribozyme on the peak level of neovascularization was tested in the mouse model described above. As shown in **Figure 10**, P7 mice were removed from the hyperoxic chamber and the mice received two intraocular injections (P12 and P13) in the right eye of 10 µg RPI.4731, the anti- *KDR/Flk-1* ribozyme. The left eye of each mouse was treated as a control and received intraocular injections of saline. Five days after being exposed to room air, neovascular nuclei in the retina of both eyes were counted. Data are presented in **Figure 11**. There was a significant decrease in retinal neovascularization (~40%) compared to the control, saline-injected eyes.

RPI.4731 sequence and chemical composition:
5'-$u_sa_sc_s$ $a_s$au uc**U** GAu Gag gcg aaa gcc Gaa Aag aca a**B**-3' (SEQ ID NO: 5978)

where:

uppercase G, A = ribonucleotides
lowercase = 2'-*O*Me
U = 2'-*C*-allyl uridine

B = inverted abasic nucleotide
S = phosphorothioate internucleotide linkage

Indications

1) Tumor angiogenesis: Angiogenesis has been shown to be necessary for tumors to grow into pathological size (Folkman, 1971, *PNAS* 76, 5217-5221; Wellstein & Czubayko, 1996, *Breast Cancer Res and Treatment* 38, 109-119). In addition, it allows tumor cells to travel through the circulatory system during metastasis. Increased levels of gene expression of a number of angiogenic factors such as vascular endothelial growth factor (VEGF) have been reported in vascularized and edema-associated brain tumors (Berkman *et al.*, 1993 *J. Clini. Invest.* 91, 153). A more direct demostration of the role of VEGF in tumor angiogenesis was demonstrated by Jim Kim *et al.*, 1993 *Nature* 362,841 wherein, monoclonal antibodies against VEGF were successfully used to inhibit the growth of rhabdomyosarcoma, glioblastoma multiforme cells in nude mice. Similarly, expression of a dominant negative mutated form of the flt-1 VEGF receptor inhibits vascularization induced by human glioblastoma cells in nude mice (Millauer *et al.*, 1994, *Nature* 367, 576). Specific tumor/cancer types that can be targeted using the nucleic acid molecules of the invention include but are not limited to the tumor/cancer types described under Diagnosis in **Table III**.

2) Ocular diseases: Neovascularization has been shown to cause or exacerbate ocular diseases including but not limited to, macular degeneration, neovascular glaucoma, diabetic retinopathy, myopic degeneration, and trachoma (Norrby, 1997, *APMIS* 105, 417-437). Aiello *et al.*, 1994 *New Engl. J. Med.* 331, 1480, showed that the ocular fluid, of a majority of patients suffering from diabetic retinopathy and other retinal disorders, contains a high concentration of VEGF. Miller *et al.*, 1994 *Am. J. Pathol.* 145, 574, reported elevated levels of VEGF mRNA in patients suffering from retinal ischemia. These observations support a direct role for VEGF in ocular diseases. Other factors including those that stimulate VEGF synthesis may also contribute to these indications.

3) Dermatological Disorders: Many indications have been identified which may by angiogenesis dependent including but not limited to psoriasis, verruca vulgaris, angiofibroma of tuberous sclerosis, pot-wine stains, Sturge Weber syndrome, Kippel-Trenaunay-Weber syndrome, and Osler-Weber-Rendu syndrome (Norrby, *supra*). Intradermal injection of the angiogenic factor b-FGF demonstrated angiogenesis in nude mice (Weckbecker et al., 1992, *Angiogenesis: Key principles-Science-Technology-Medicine*, ed R. Steiner) Detmar *et al.*, 1994 *J. Exp. Med.* 180, 1141 reported that VEGF and its receptors were over-expressed in

psoriatic skin and psoriatic dermal microvessels, suggesting that VEGF plays a significant role in psoriasis.

4) Rheumatoid arthritis: Immunohistochemistry and *in situ* hybridization studies on tissues from the joints of patients suffering from rheumatoid arthritis show an increased level of VEGF and its receptors (Fava *et al.*, 1994 *J. Exp. Med.* 180, 341). Additionally, Koch *et al.*, 1994 *J. Immunol.* 152, 4149, found that VEGF-specific antibodies were able to significantly reduce the mitogenic activity of synovial tissues from patients suffering from rheumatoid arthritis. These observations support a direct role for VEGF in rheumatoid arthritis. Other angiogenic factors including those of the present invention may also be involved in arthritis.

5) Endometriosis: Various studies indicate that VEGF is directly implicated in endometriosis. In one study, VEGF concentrations measured by ELISA in peritoneal fluid were found to be significantly higher in women with endometriosis than in women without endometriosis (24.1 ± 15 ng/ml vs 13.3 ± 7.2 ng/ml in normals). In patients with endometriosis, higher concentrations of VEGF were detected in the proliferative phase of the menstrual cycle (33 ± 13 ng/ml) compared to the secretory phase (10.7 ± 5 ng/ml). The cyclic variation was not noted in fluid from normal patients (McLaren *et al.*, 1996, *Human Reprod.* 11, 220-223). In another study, women with moderate to severe endometriosis had significantly higher concentrations of peritoneal fluid VEGF than women without endometriosis. There was a positive correlation between the severity of endometriosis and the concentration of VEGF in peritoneal fluid. In human endometrial biopsies, VEGF expression increased relative to the early proliferative phase approximately 1.6-, 2-, and 3.6-fold in midproliferative, late proliferative, and secretory endometrium (Shifren *et al.*, 1996, *J. Clin. Endocrinol. Metab.* 81, 3112-3118).

In a third study, VEGF-positive staining of human ectopic endometrium was shown to be localized to macrophages (double immunofluorescent staining with CD14 marker). Peritoneal fluid macrophages demonstrated VEGF staining in women with and without endometriosis. However, increased activation of macrophages (acid phosphatatse activity) was demonstrated in fluid from women with endometriosis compared with controls. Peritoneal fluid macrophage conditioned media from patients with endometriosis resulted in significantly increased cell proliferation ([^{3}H] thymidine incorporation) in HUVEC cells compared to controls. The percentage of peritoneal fluid macrophages with VEGFR2 mRNA was higher during the secretory phase, and significantly higher in fluid from women with endometriosis (80 ± 15%) compared with controls (32 ± 20%). Flt-mRNA was detected in

peritoneal fluid macrophages from women with and without endometriosis, but there was no difference between the groups or any evidence of cyclic dependence (McLaren *et al.*, 1996, *J. Clin. Invest.* 98, 482-489).

In the early proliferative phase of the menstrual cycle, VEGF has been found to be expressed in secretory columnar epithelium (estrogen-responsive) lining both the oviducts and the uterus in female mice. During the secretory phase, VEGF expression was shown to have shifted to the underlying stroma composing the functional endometrium. In addition to examining the endometrium, neovascularization of ovarian follicles and the corpus luteum, as well as angiogenesis in embryonic implantation sites have been analyzed. For these processes, VEGF was expressed in spatial and temporal proximity to forming vasculature (Shweiki *et al.*, 1993, *J. Clin. Invest.* 91, 2235-2243).

The present body of knowledge in VEGFR1 and/or VEGFR2 research indicates the need for methods to assay VEGFR1 and/or VEGFR2 activity and for compounds that can regulate VEGFR1 and/or VEGFR2 expression for research, diagnostic, and therapeutic use. As described herein, the nucleic acid molecules of the present invention can be used in assays to diagnose disease state related of VEGF, VEGFR1 and/or VEGFR2 levels. In addition, the nucleic acid molecules can be used to treat disease state related to VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 levels.

Particular processes, diseases, or conditions that can be associated with VEGFR1 and/or VEGFR2 levels include, but are not limited to, gynecologic neovascularization, such as endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), menopausal dysfunction, other diseases and conditions discussed herein, and other diseases or conditions that are related to or respond to the levels of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2, in a cell or tissue, alone or in combination with other therapies

The use of GnRH (gonadotropin releasing hormone) agonists, Lupron Depot (Leuprolide Acetate), Synarel (naferalin acetate), Zolodex (goserelin acetate), Suprefact (buserelin acetate), Danazol, or oral contraceptives including, but not limited to, Depo-Provera or Provera (medroxyprogesterone acetate), or any other estrogen/progesterone contraceptive, are all non-limiting examples of compounds and methods that can be combined with or used in conjunction with the nucleic acid molecules of the instant invention. Various chemotherapies can be readily combined with nucleic acid molecules of the invention for the treatment of endometrial carcinoma. Common chemotherapies that can be combined with nucleic acid molecules of the instant invention include various combinations of cytotoxic drugs to kill the

cancer cells. These drugs include but are not limited to paclitaxel (Taxol), docetaxel, cisplatin, methotrexate, cyclophosphamide, doxorubin, fluorouracil carboplatin, edatrexate, gemcitabine, vinorelbine *etc.* Those skilled in the art will recognize that other drug compounds and therapies can be readily combined with the nucleic acid molecules of the instant invention and are hence within the scope of the instant invention.

Animal Models

There are several animal models in which the anti-angiogenesis effect of nucleic acids of the present invention, such as ribozymes, directed against VEGF-R mRNAs can be tested. Typically, a corneal model has been used to study angiogenesis in rat and rabbit since recruitment of vessels can easily be followed in this normally avascular tissue (Pandey *et al.*, 1995 *Science* 268: 567-569). In these models, a small Teflon or Hydron disk pretreated with an angiogenesis factor (e.g. bFGF or VEGF) is inserted into a pocket surgically created in the cornea. Angiogenesis is monitored 3 to 5 days later. Ribozymes directed against VEGF-R mRNAs would be delivered in the disk as well, or dropwise to the eye over the time course of the experiment. In another eye model, hypoxia has been shown to cause both increased expression of VEGF and neovascularization in the retina (Pierce *et al.*, 1995 *Proc. Natl. Acad. Sci.* USA. 92: 905-909; Shweiki *et al.*, 1992 *J. Clin. Invest.* 91: 2235-2243).

In human glioblastomas, it has been shown that VEGF is at least partially responsible for tumor angiogenesis (Plate *et al.*, 1992 *Nature* 359, 845). Animal models have been developed in which glioblastoma cells are implanted subcutaneously into nude mice and the progress of tumor growth and angiogenesism is studied (Kim *et al.*, 1993 *supra;* Millauer *et al.*, 1994 *supra*).

Another animal model that addresses neovascularization involves Matrigel, an extract of basement membrane that becomes a solid gel when injected subcutaneously (Passaniti *et al.*, 1992 *Lab. Invest.* 67: 519-528). When the Matrigel is supplemented with angiogenesis factors such as VEGF, vessels grow into the Matrigel over a period of 3 to 5 days and angiogenesis can be assessed. Ribozymes directed against VEGF-R mRNAs can be delivered in the Matrigel to assess anti-angiogesis effect.

Several animal models exist for screening of anti-angiogenic agents. These include corneal vessel formation following corneal injury (Burger *et al.*, 1985 *Cornea* 4: 35-41; Lepri, *et al.*, 1994 *J. Ocular Pharmacol.* 10: 273-280; Ormerod *et al.*, 1990 *Am. J. Pathol.* 137: 1243-1252) or intracorneal growth factor implant (Grant *et al.*, 1993 *Diabetologia* 36: 282-291; Pandey *et al.* 1995 *supra;* Zieche *et al.*, 1992 *Lab. Invest.* 67: 711-715), vessel

growth into Matrigel matrix containing growth factors (Passaniti *et al.*, 1992 *supra*), female reproductive organ neovascularization following hormonal manipulation (Shweiki *et al.*, 1993 *Clin. Invest.* 91: 2235-2243), several models involving inhibition of tumor growth in highly vascularized solid tumors (O'Reilly *et al.*, 1994 *Cell* 79: 315-328; Senger *et al.*, 1993 *Cancer and Metas. Rev.* 12: 303-324; Takahasi *et al.*, 1994 *Cancer Res.* 54: 4233-4237; Kim *et al.*, 1993 *supra*), and transient hypoxia-induced neovascularization in the mouse retina (Pierce *et al.*, 1995 *Proc. Natl. Acad. Sci.* USA. 92: 905-909).

The cornea model, described in Pandey et al. *supra*, is the most common and well characterized anti-angiogenic agent efficacy screening model. This model involves an avascular tissue into which vessels are recruited by a stimulating agent (growth factor, thermal or alkalai burn, endotoxin). The corneal model utilizes the intrastromal corneal implantation of a Teflon pellet soaked in a VEGF-Hydron solution to recruit blood vessels toward the pellet which can be quantitated using standard microscopic and image analysis techniques. To evaluate their anti-angiogenic efficacy, ribozymes are applied topically to the eye or bound within Hydron on the Teflon pellet itself. This avascular cornea as well as the Matrigel (see below) provide for low background assays. While the corneal model has been performed extensively in the rabbit, studies in the rat have also been conducted.

The mouse model (Passaniti et al., *supra*) is a non-tissue model which utilizes Matrigel, an extract of basement membrane (Kleinman et al., 1986) or Millipore® filter disk, which can be impregnated with growth factors and anti-angiogenic agents in a liquid form prior to injection. Upon subcutaneous administration at body temperature, the Matrigel or Millipore® filter disk forms a solid implant. VEGF embedded in the Matrigel or Millipore® filter disk would be used to recruit vessels within the matrix of the Matrigel or Millipore® filter disk which can be processed histologically for endothelial cell specific vWF (factor VIII antigen) immunohistochemistry, Trichrome-Masson stain, or hemoglobin content. Like the cornea, the Matrigel or Millipore® filter disk are avascular; however, it is not tissue. In the Matrigel or Millipore® filter disk model, ribozymes are administered within the matrix of the Matrigel or Millipore® filter disk to test their anti-angiogenic efficacy. Thus, delivery issues in this model, as with delivery of ribozymes by Hydron- coated Teflon pellets in the rat cornea model, are minimized due to the homogeneous presence of the ribozyme within the respective matrix.

These models offer a distinct advantage over several other angiogenic models listed previously. The ability to use VEGF as a pro-angiogenic stimulus in both models is highly desirable since ribozymes target only VEGFr mRNA. In other words, the involvement of

other non-specific types of stimuli in the cornea and Matrigel models is not advantageous from the standpoint of understanding the pharmacologic mechanism by which the anti-VEGFr mRNA ribozymes produce their effects. In addition, the models allow for testing the specificity of the anti-VEGFr mRNA ribozymes by using either aFGF or bFGF as a pro-angiogenic factor. Vessel recruitment using FGF should not be affected in either model by anti-VEGFr mRNA ribozymes. Other models of angiogenesis, including vessel formation in the female reproductive system using hormonal manipulation (Shweiki *et al.*, 1993 *supra*); a variety of vascular solid tumor models which involve indirect correlations with angiogenesis (O'Reilly *et al.*, 1994 *supra*; Senger *et al.*, 1993 *supra*; Takahasi *et al.*, 1994 *supra*; Kim *et al.*, 1993 *supra*); and retinal neovascularization following transient hypoxia (Pierce *et al.*, 1995 *supra*), were not selected for efficacy screening due to their non-specific nature, although they can be useful models due to a demonstrated correlation between VEGF and angiogenesis.

Other model systems to study tumor angiogenesis is reviewed by Folkman, 1985 *Adv. Cancer. Res.*. 43, 175.

Use of murine models

For a typical systemic study involving 10 mice (20 g each) per dose group, 5 doses (1, 3, 10, 30 and 100 mg/kg daily over 14 days continuous administration), approximately 400 mg of ribozyme, formulated in saline would be used. A similar study in young adult rats (200 g) would require over 4 g. Parallel pharmacokinetic studies involve the use of similar quantities of ribozymes further justifying the use of murine models.

Ribozymes and Lewis lung carcinoma and B-16 melanoma murine models

Identifying a common animal model for systemic efficacy testing of ribozymes is an efficient way of screening ribozymes for systemic efficacy.

The Lewis lung carcinoma and B-16 murine melanoma models are well accepted models of primary and metastatic cancer and are used for initial screening of anti-cancer agents. These murine models are not dependent upon the use of immunodeficient mice, are relatively inexpensive, and minimize housing concerns. Both the Lewis lung and B-16 melanoma models involve subcutaneous implantation of approximately 10^6 tumor cells from metastatically aggressive tumor cell lines (Lewis lung lines 3LL or D122, LLc-LN7; B-16-BL6 melanoma) in C57BL/6J mice. Alternatively, the Lewis lung model can be produced by the surgical implantation of tumor spheres (approximately 0.8 mm in diameter). Metastasis

also can be modeled by injecting the tumor cells directly intraveneously. In the Lewis lung model, microscopic metastases can be observed approximately 14 days following implantation with quantifiable macroscopic metastatic tumors developing within 21-25 days. The B-16 melanoma exhibits a similar time course with tumor neovascularization beginning 4 days following implantation. Since both primary and metastatic tumors exist in these models after 21-25 days in the same animal, multiple measurements can be taken as indices of efficacy. Primary tumor volume and growth latency as well as the number of micro- and macroscopic metastatic lung foci or number of animals exhibiting metastases can be quantitated. The percent increase in lifespan can also be measured. Thus, these models provide suitable primary efficacy assays for screening systemically administered ribozymes/ribozyme formulations.

In the Lewis lung and B-16 melanoma models, systemic pharmacotherapy with a wide variety of agents usually begins 1-7 days following tumor implantation/inoculation with either continuous or multiple administration regimens. Concurrent pharmacokinetic studies can be performed to determine whether sufficient tissue levels of ribozymes can be achieved for pharmacodynamic effect to be expected. Furthermore, primary tumors and secondary lung metastases can be removed and subjected to a variety of *in vitro* studies (*i.e.* target RNA reduction).

Flt-1, KDR and/or flk-1 protein levels can be measured clinically or experimentally by FACS analysis. Flt-1, KDR and/or flk-1 encoded mRNA levels can be assessed by Northern analysis, RNase-protection, primer extension analysis and/or quantitative RT-PCR. Ribozymes that block flt-1, KDR and/or flk-1 protein encoding mRNAs and therefore result in decreased levels of flt-1, KDR and/or flk-1 activity by more than 20% *in vitro* can be identified.

Ribozymes and/or genes encoding them are delivered by either free delivery, liposome delivery, cationic lipid delivery, adeno-associated virus vector delivery, adenovirus vector delivery, retrovirus vector delivery or plasmid vector delivery in these animal model experiments (see above).

Subjects can be treated by locally administering nucleic acids targeted against VEGF-R by direct injection. Routes of administration include, but are not limited to, intravascular, intramuscular, subcutaneous, intraarticular, aerosol inhalation, oral (tablet, capsule or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery.

Surgically induced models of endometriosis have been developed in rats, mice, and rabbits. Non-human primates demonstrate spontaneous endometriosis, but surgical induction can also be used. In addition to the surgical technique, cycle monitoring can be performed by daily vaginal cytology in primates. For all of the surgically induced models of endometriosis, the following general procedure is used. An initial laparotomy is performed to implant tissue from a donor animal. A portion of one uterine horn (or one complete horn in the case of mice) is removed. The endometrium of this piece of uterus is separated from the myometrium and cut into small segments (4-10 mm2). Segments (approximately 3) are sutured to various locations within the abdominal cavity (peritoneum, intestinal mesentery vessels, uterus, broad ligament). Cummings and Metcalf (1996) attached whole segments of mouse uterus without separating the endometrium from the myometrium. Implants are allowed to grow for 3-6 weeks. A second laparotomy is sometimes performed to verify development of endometriosis-like foci (vascularization and cysts filled with clear fluid). This second laparotomy was done in the studies by Quereda *et al.*, (1996) and Stoeckemann *et al.*, (1995). After 3-6 weeks post-surgery and/or following visualization of endometriosis, drug treatment is initiated and continued for a prescribed period of time. At the termination of these studies, animals are euthanized. Endpoints include, but are not limited to, changes in the surface area of the implants and tissue mass of the ectopic endometrial implants (see for example Brogniez *et al.*, 1995, *Human Reprod.* 10, 927-931; Cummings *et al.*, 1996, *Tox. Appl. Pharm.* 138, 131-139; Cummings and Metcalf, 1996, *Proc. Soc. Exp. Biol. Med.* 212, 332-337; D'Hooghe *et al.*, 1996, *Fertility and Sterility.* 66, 809-813; Quereda *et al.*, 1996, *Eur. J. Obstet. Gynecol. Rep. Biol.* 67, 35-40; and Stoeckemann *et al.*, 1995, *Human Reprod.* 10, 3264-3271).

Combination therapies

Gemcytabine and cyclophosphamide are non-limiting examples of chemotherapeutic agents that can be combined with or used in conjunction with the nucleic acid molecules (*e.g.* ribozymes and antisense molecules) of the instant invention. Those skilled in the art will recognize that other anti-angiogenic and/or anti-cancer compounds and therapies can be similarly be readily combined with the nucleic acid molecules of the instant invention (*e.g.* ribozymes and antisense molecules) and are hence within the scope of the instant invention. Such compounds and therapies are well known in the art (see for example Cancer: Principles

and Pranctice of Oncology, Volumes 1 and 2, eds Devita, V.T., Hellman, S., and Rosenberg, S.A., J.B. Lippincott Company, Philadelphia, USA; incorporated herein by reference) and include, without limitations, folates, antifolates, pyrimidine analogs, fluoropyrimidines, purine analogs, adenosine analogs, topoisomerase I inhibitors, anthrapyrazoles, retinoids, antibiotics, anthacyclins, platinum analogs, alkylating agents, nitrosoureas, plant derived compounds such as vinca alkaloids, epipodophyllotoxins, tyrosine kinase inhibitors, taxols, radiation therapy, surgery, nutritional supplements, gene therapy, radiotherapy, for example 3D-CRT, immunotoxin therapy, for example ricin, and monoclonal antibodies. Specific examples of chemotherapeutic compounds than can be combined with or used in conjuction with the nucleic acid molecules of the invention include but are not limited to Paclitaxel; Docetaxel; Methotrexate; Doxorubin; Edatrexate; Vinorelbine; Tomaxifen; Leucovorin; 5-fluoro uridine (5-FU); Irinotecan (CAMPTOSAR® or CPT-11 or Camptothecin-11 or Campto); Cisplatin; Carboplatin; Amsacrine; Cytarabine; Bleomycin; Mitomycin C; Dactinomycin; Mithramycin; Hexamethylmelamine; Dacarbazine; L-asperginase; Nitrogen mustard; Melphalan, Chlorambucil; Busulfan; Ifosfamide; 4-hydroperoxycyclophosphamide, Thiotepa; Tamoxifen, Herceptin; IMC C225; ABX-EGF: and combinations thereof.

Diagnostic uses

The nucleic acid molecules of this invention (*e.g.*, enzymatic nucleic acid molecules) can be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of VEGF and/or VEGFr, such as VEGFR1 and/or VEGFR2 RNA in a cell. The close relationship between enzymatic nucleic acid molecule activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple enzymatic nucleic acid molecules described in this invention, one can map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with enzymatic nucleic acid molecules can be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets can be defined as important mediators of the disease. These experiments can lead to better treatment of the disease progression by affording the possibility of combinational therapies (*e.g.*, multiple enzymatic nucleic acid molecules targeted to different genes, enzymatic nucleic acid molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations of enzymatic nucleic acid molecules and/or other chemical or biological molecules). Other *in*

vitro uses of enzymatic nucleic acid molecules of this invention are well known in the art, and include detection of the presence of mRNAs associated with VEGF, VEGFR1 and/or VEGFR2-related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with an enzymatic nucleic acid molecule using standard methodology.

In a specific example, enzymatic nucleic acid molecules which cleave only wild-type or mutant forms of the target RNA are used for the assay. The first enzymatic nucleic acid molecule is used to identify wild-type RNA present in the sample and the second enzymatic nucleic acid molecule is used to identify mutant RNA in the sample. As reaction controls, synthetic substrates of both wild-type and mutant RNA are cleaved by both enzymatic nucleic acid molecules to demonstrate the relative enzymatic nucleic acid molecule efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus each analysis requires two enzymatic nucleic acid molecules, two substrates and one unknown sample which is combined into six reactions. The presence of cleavage products is determined using an RNAse protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, VEGFR1 and/or VEGFR2) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels will be adequate and will decrease the cost of the initial diagnosis. Higher mutant form to wild-type ratios are correlated with higher risk whether RNA levels are compared qualitatively or quantitatively. The use of enzymatic nucleic acid molecules in diagnostic applications contemplated by the instant invention is described, for example, in Usman *et al.*, US Patent Application No. 09/877,526, George *et al.*, US Patent Nos. 5,834,186 and 5,741,679, Shih *et al.*, US Patent No. 5,589,332, Nathan *et al.*, US Patent No 5,871,914, Nathan and Ellington, International PCT publication No. WO 00/24931, Breaker *et al.*, International PCT Publication Nos. WO 00/26226 and 98/27104, and Sullenger *et al.*, US Patent Application Serial No. 09/205,520.

Additional Uses

Uses of sequence-specific enzymatic nucleic acid molecules of the instant invention can have many of the same applications for the study of RNA that DNA restriction endonucleases have for the study of DNA (Nathans *et al.*, 1975 *Ann. Rev. Biochem.* 44:273). For example,

the pattern of restriction fragments can be used to establish sequence relationships between two related RNAs, and large RNAs can be specifically cleaved to fragments of a size more useful for study. The ability to engineer sequence specificity of the enzymatic nucleic acid molecule is ideal for cleavage of RNAs of unknown sequence. Applicant has described the use of nucleic acid molecules to down-regulate gene expression of target genes in bacterial, microbial, fungal, viral, and eukaryotic systems including plant, or mammalian cells.

All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Other embodiments are within the following claims.

TABLE I

Characteristics of Ribozymes

Group I Introns
Size: ~200 to >1000 nucleotides.
Requires a U in the target sequence immediately 5' of the cleavage site.
Binds 4-6 nucleotides at 5' side of cleavage site.
Over 75 known members of this class. Found in *Tetrahymena thermophila* rRNA, fungal mitochondria, chloroplasts, phage T4, blue-green algae, and others.

RNAseP RNA (M1 RNA)
Size: ~290 to 400 nucleotides.
RNA portion of a ribonucleoprotein enzyme. Cleaves tRNA precursors to form mature tRNA.
Roughly 10 known members of this group all are bacterial in origin.

Hammerhead Ribozyme
Size: ~13 to 40 nucleotides.
Requires the target sequence UH immediately 5' of the cleavage site.
Binds a variable number of nucleotides on both sides of the cleavage site.
14 known members of this class. Found in a number of plant pathogens (virusoids) that use RNA as the infectious agent (Figure 1 and 2)

Hairpin Ribozyme
Size: ~50 nucleotides.
Requires the target sequence GUC immediately 3' of the cleavage site.
Binds 4-6 nucleotides at 5' side of the cleavage site and a variable number to the 3' side of the cleavage site.
Only 3 known member of this class. Found in three plant pathogen (satellite RNAs of the tobacco ringspot virus, arabis mosaic virus and chicory yellow mottle virus) which uses RNA as the infectious agent (Figure 3).

Hepatitis Delta Virus (HDV) Ribozyme
Size: 50 - 60 nucleotides (at present).
Sequence requirements not fully determined.
Binding sites and structural requirements not fully determined, although no sequences 5' of cleavage site are required.
Only 1 known member of this class. Found in human HDV (Figure 4).

***Neurospora* VS RNA Ribozyme**

Size: ~144 nucleotides (at present)

Cleavage of target RNAs recently demonstrated.
Sequence requirements not fully determined.
Binding sites and structural requirements not fully determined. Only 1 known member of this class. Found in *Neurospora* VS RNA (Figure 5).

Table II:

A. 2.5 µmol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time* RNA
Phosphoramidites	6.5	163 µL	45 sec	2.5 min	7.5 min
S-Ethyl Tetrazole	23.8	238 µL	45 sec	2.5 min	7.5 min
Acetic Anhydride	100	233 µL	5 sec	5 sec	5 sec
N-Methyl Imidazole	186	233 µL	5 sec	5 sec	5 sec
TCA	176	2.3 mL	21 sec	21 sec	21 sec
Iodine	11.2	1.7 mL	45 sec	45 sec	45 sec
Beaucage	12.9	645 µL	100 sec	300 sec	300 sec
Acetonitrile	NA	6.67 mL	NA	NA	NA

B. 0.2 µmol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time* RNA
Phosphoramidites	15	31 µL	45 sec	233 sec	465 sec
S-Ethyl Tetrazole	38.7	31 µL	45 sec	233 min	465 sec
Acetic Anhydride	655	124 µL	5 sec	5 sec	5 sec
N-Methyl Imidazole	1245	124 µL	5 sec	5 sec	5 sec
TCA	700	732 µL	10 sec	10 sec	10 sec
Iodine	20.6	244 µL	15 sec	15 sec	15 sec

Beaucage	7.7	232 µL	100 sec	300 sec	300 sec
Acetonitrile	NA	2.64 mL	NA	NA	NA

C. 0.2 µmol Synthesis Cycle 96 well Instrument

Reagent	Equivalents DNA/2'-O-methyl/Ribo	Amount DNA/2'-O-methyl/Ribo	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time* Ribo
Phosphoramidites	22/33/66	40/60/120 µL	60 sec	180 sec	360sec
S-Ethyl Tetrazole	70/105/210	40/60/120 µL	60 sec	180 min	360 sec
Acetic Anhydride	265/265/265	50/50/50 µL	10 sec	10 sec	10 sec
N-Methyl Imidazole	502/502/502	50/50/50 µL	10 sec	10 sec	10 sec
TCA	238/475/475	250/500/500 µL	15 sec	15 sec	15 sec
Iodine	6.8/6.8/6.8	80/80/80 µL	30 sec	30 sec	30 sec
Beaucage	34/51/51	80/120/120	100 sec	200 sec	200 sec
Acetonitrile	NA	1150/1150/1150 µL	NA	NA	NA

*** Wait time does not include contact time during delivery.**

Table III: Patient Demographics

Dose cohort (mg/m²)	Pt#	Age	Sex	Diagnosis	Doses
10	1001	49	F	NSC Lung	29
10	1002	65	F	liposarcoma	120
10	1003	49	M	nasopharyngeal CA	109
30	1004	35	M	non-small cell lung	1
30	1005	45	F	melanoma (ocular)	113
30	1006	57	M	colon	199
30	1007	39	F	epitheliod hemangioendothelioma	198
100	1008	52	M	adrenal CA	57
100	1009	44	F	breast	35
100	1010	62	F	renal	134
300	1011	24	F	melanoma	31
300	1012	57	M	renal cell	178
300	1013	53	M	nasopharyngeal SCCA	29
300	1014	64	F	peritoneal mesothelioma	324
100	1015	65	M	melanoma	140
100	1016	77	F	breast	265
100	1017		F	melanoma	35
100	1018	26	F	melanoma	7
100	1019	69	F	endometrial sarcoma	500
100	1020	65	M	carcinoid	124
100	1021	59	M	gallbladder adeno carcinoma	34
100	1022	43	M	colorectal	8
100	1023	78	F	breast	50
100	1024	40	F	parotid adenocarcinoma	285
100	1025	52	F	breast	71
100	1026	39	F	breast	34
100	1027	55	F	breast	36
100	1028	52	M	melanoma	29
100	1029	38	M	pancreatic	36
100	1030	83	M	melanoma	41
100	1031	50	M	medullary thyroid	108

One patient taken off study due to progressive disease. Allowed to resume ANGIOZYME on a compassionate basis.

As of September 1, 2001, all patients were off study. (Although one patient resumed treatment per above note)

Table IV Pharmacokinetic parameters of ANGIOZYME after bolus subcutaneous administration.

		10 mg/m²		30 mg/m²		100 mg/m²		300 mg/m²	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 1	Cmax (ug/mL)	0.43	0.07	0.62	0.28	3.17	0.69	8.91	2.93
	AUCt (ug*hr/mL)	2.60	1.43	6.04	2.70	34.14	2.28	89.87	21.68
	AUCinf (ug*hr/mL)	4.40	0.06	7.99	1.66	37.51	1.91	101.57	13.47
	t(1/2) (hr)	3.62	0.79	7.32	6.94	4.58	0.02	9.26	6.20
	CL/F (L/hr/m²)	2.24	0.08	3.73	0.92	2.96	0.61	2.99	0.43
Day 29	Cmax (ug/mL)	0.35	0.19	1.17	0.53	3.23	0.35	8.93	6.71
	AUCt (ug*hr/mL)	2.11	1.31	7.29	1.16	31.87	1.91	119.42	65.84
	AUCinf (ug*hr/mL)	3.38	1.31	8.54	2.46	33.61	2.16	132.73	67.82
	t(1/2) (hr)	4.49	1.60	3.26	1.01	4.66	0.35	7.24	0.70
	CL/F (L/hr/m²)	2.49	1.48	3.69	0.94	3.21	0.56	2.72	1.40

Table V: Human FLT DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID No	DNAzyme	Seq ID No
17	UCCUCUCG G CUCCUCCC	1	GGGAGGAG GGCTAGCTACAACGA CGAGAGGA	1703
28	CCUCCCCG G CAGCGGCG	2	CGCCGCTG GGCTAGCTACAACGA CGGGGAGG	1704
31	CCCCGGCA G CGGCGGCG	3	CGCCGCCG GGCTAGCTACAACGA TGCCGGGG	1705
34	CGGCAGCG G CGGCGGCU	4	AGCCGCCG GGCTAGCTACAACGA CGCTGCCG	1706
37	CAGCGGCG G CGGCUCGG	5	CCGAGCCG GGCTAGCTACAACGA CGCCGCTG	1707
40	CGGCGGCG G CUCGGAGC	6	GCTCCGAG GGCTAGCTACAACGA CGCCGCCG	1708
47	GGCUCGGA G CGGGCUCC	7	GGAGCCCG GGCTAGCTACAACGA TCCGAGCC	1709
51	CGGAGCGG G CUCCGGGG	8	CCCCGGAG GGCTAGCTACAACGA CCGCTCCG	1710
59	GCUCCGGG G CUCGGGUG	9	CACCCGAG GGCTAGCTACAACGA CCCGGAGC	1711
65	GGGCUCGG G UGCAGCGG	10	CCGCTGCA GGCTAGCTACAACGA CCGAGCCC	1712
67	GCUCGGGU G CAGCGGCC	11	GGCCGCTG GGCTAGCTACAACGA ACCCGAGC	1713
70	CGGGUGCA G CGGCCAGC	12	GCTGGCCG GGCTAGCTACAACGA TGCACCCG	1714
73	GUGCAGCG G CCAGCGGG	13	CCCGCTGG GGCTAGCTACAACGA CGCTGCAC	1715
77	AGCGGCCA G CGGGCCUG	14	CAGGCCCG GGCTAGCTACAACGA TGGCCGCT	1716
81	GCCAGCGG G CCUGGCGG	15	CCGCCAGG GGCTAGCTACAACGA CCGCTGGC	1717
86	CGGGCCUG G CGGCGAGG	16	CCTCGCCG GGCTAGCTACAACGA CAGGCCCG	1718
89	GCCUGGCG G CGAGGAUU	17	AATCCTCG GGCTAGCTACAACGA CGCCAGGC	1719
95	CGGCGAGG A UUACCCGG	18	CCGGGTAA GGCTAGCTACAACGA CCTCGCCG	1720
98	CGAGGAUU A CCCGGGGA	19	TCCCCGGG GGCTAGCTACAACGA AATCCTCG	1721
108	CCGGGGAA G UGGUUGUC	20	GACAACCA GGCTAGCTACAACGA TTCCCCGG	1722
111	GGGAAGUG G UUGUCUCC	21	GGAGACAA GGCTAGCTACAACGA CACTTCCC	1723
114	AAGUGGUU G UCUCCUGG	22	CCAGGAGA GGCTAGCTACAACGA AACCACTT	1724
122	GUCUCCUG G CUGGAGCC	23	GGCTCCAG GGCTAGCTACAACGA CAGGAGAC	1725
128	UGGCUGGA G CCGCGAGA	24	TCTCGCGG GGCTAGCTACAACGA TCCAGCCA	1726
131	CUGGAGCC G CGAGACGG	25	CCGTCTCG GGCTAGCTACAACGA GGCTCCAG	1727
136	GCCGCGAG A CGGGCGCU	26	AGCGCCCG GGCTAGCTACAACGA CTCGCGGC	1728
140	CGAGACGG G CGCUCAGG	27	CCTGAGCG GGCTAGCTACAACGA CCGTCTCG	1729
142	AGACGGGC G CUCAGGGC	28	GCCCTGAG GGCTAGCTACAACGA GCCCGTCT	1730
149	CGCUCAGG G CGCGGGGC	29	GCCCCGCG GGCTAGCTACAACGA CCTGAGCG	1731
151	CUCAGGGC G CGGGGCCG	30	CGGCCCCG GGCTAGCTACAACGA GCCCTGAG	1732
156	GGCGCGGG G CCGGCGGC	31	GCCGCCGG GGCTAGCTACAACGA CCCGCGCC	1733
160	CGGGGCCG G CGGCGGCG	32	CGCCGCCG GGCTAGCTACAACGA CGGCCCCG	1734
163	GGCCGGCG G CGGCGAAC	33	GTTCGCCG GGCTAGCTACAACGA CGCCGGCC	1735
166	CGGCGGCG G CGAACGAG	34	CTCGTTCG GGCTAGCTACAACGA CGCCGCCG	1736
170	GGCGGCGA A CGAGAGGA	35	TCCTCTCG GGCTAGCTACAACGA TCGCCGCC	1737
178	ACGAGAGG A CGGACUCU	36	AGAGTCCG GGCTAGCTACAACGA CCTCTCGT	1738
182	GAGGACGG A CUCUGGCG	37	CGCCAGAG GGCTAGCTACAACGA CCGTCCTC	1739
188	GGACUCUG G CGGCCGGG	38	CCCGGCCG GGCTAGCTACAACGA CAGAGTCC	1740
191	CUCUGGCG G CCGGGUCG	39	CGACCCGG GGCTAGCTACAACGA CGCCAGAG	1741
196	GCGGCCGG G UCGUUGGC	40	GCCAACGA GGCTAGCTACAACGA CCGGCCGC	1742
199	GCCGGGUC G UUGGCCGG	41	CCGGCCAA GGCTAGCTACAACGA GACCCGGC	1743
203	GGUCGUUG G CCGGGGGA	42	TCCCCCGG GGCTAGCTACAACGA CAACGACC	1744
212	CCGGGGGA G CGCGGGCA	43	TGCCCGCG GGCTAGCTACAACGA TCCCCCGG	1745
214	GGGGGAGC G CGGGCACC	44	GGTGCCCG GGCTAGCTACAACGA GCTCCCCC	1746
218	GAGCGCGG G CACCGGGC	45	GCCCGGTG GGCTAGCTACAACGA CCGCGCTC	1747
220	GCGCGGGC A CCGGGCGA	46	TCGCCCGG GGCTAGCTACAACGA GCCCGCGC	1748
225	GGCACCGG G CGAGCAGG	47	CCTGCTCG GGCTAGCTACAACGA CCGGTGCC	1749
229	CCGGGCGA G CAGGCCGC	48	GCGGCCTG GGCTAGCTACAACGA TCGCCCGG	1750

233	GCGAGCAG G CCGCGUCG	49	CGACGCGG GGCTAGCTACAACGA CTGCTCGC	1751
236	AGCAGGCC G CGUCGCGC	50	GCGCGACG GGCTAGCTACAACGA GGCCTGCT	1752
238	CAGGCCGC G UCGCGCUC	51	GAGCGCGA GGCTAGCTACAACGA GCGGCCTG	1753
241	GCCGCGUC G CGCUCACC	52	GGTGAGCG GGCTAGCTACAACGA GACGCGGC	1754
243	CGCGUCGC G CUCACCAU	53	ATGGTGAG GGCTAGCTACAACGA GCGACGCG	1755
247	UCGCGCUC A CCAUGGUC	54	GACCATGG GGCTAGCTACAACGA GAGCGCGA	1756
250	CGCUCACC A UGGUCAGC	55	GCTGACCA GGCTAGCTACAACGA GGTGAGCG	1757
253	UCACCAUG G UCAGCUAC	56	GTAGCTGA GGCTAGCTACAACGA CATGGTGA	1758
257	CAUGGUCA G CUACUGGG	57	CCCAGTAG GGCTAGCTACAACGA TGACCATG	1759
260	GGUCAGCU A CUGGGACA	58	TGTCCCAG GGCTAGCTACAACGA AGCTGACC	1760
266	CUACUGGG A CACCGGGG	59	CCCCGGTG GGCTAGCTACAACGA CCCAGTAG	1761
268	ACUGGGAC A CCGGGGUC	60	GACCCCGG GGCTAGCTACAACGA GTCCCAGT	1762
274	ACACCGGG G UCCUGCUG	61	CAGCAGGA GGCTAGCTACAACGA CCCGGTGT	1763
279	GGGGUCCU G CUGUGCGC	62	GCGCACAG GGCTAGCTACAACGA AGGACCCC	1764
282	GUCCUGCU G UGCGCGCU	63	AGCGCGCA GGCTAGCTACAACGA AGCAGGAC	1765
284	CCUGCUGU G CGCGCUGC	64	GCAGCGCG GGCTAGCTACAACGA ACAGCAGG	1766
286	UGCUGUGC G CGCUGCUC	65	GAGCAGCG GGCTAGCTACAACGA GCACAGCA	1767
288	CUGUGCGC G CUGCUCAG	66	CTGAGCAG GGCTAGCTACAACGA GCGCACAG	1768
291	UGCGCGCU G CUCAGCUG	67	CAGCTGAG GGCTAGCTACAACGA AGCGCGCA	1769
296	GCUGCUCA G CUGUCUGC	68	GCAGACAG GGCTAGCTACAACGA TGAGCAGC	1770
299	GCUCAGCU G UCUGCUUC	69	GAAGCAGA GGCTAGCTACAACGA AGCTGAGC	1771
303	AGCUGUCU G CUUCUCAC	70	GTGAGAAG GGCTAGCTACAACGA AGACAGCT	1772
310	UGCUUCUC A CAGGAUCU	71	AGATCCTG GGCTAGCTACAACGA GAGAAGCA	1773
315	CUCACAGG A UCUAGUUC	72	GAACTAGA GGCTAGCTACAACGA CCTGTGAG	1774
320	AGGAUCUA G UUCAGGUU	73	AACCTGAA GGCTAGCTACAACGA TAGATCCT	1775
326	UAGUUCAG G UUCAAAAU	74	ATTTTGAA GGCTAGCTACAACGA CTGAACTA	1776
333	GGUUCAAA A UUAAAAGA	75	TCTTTTAA GGCTAGCTACAACGA TTTGAACC	1777
341	AUUAAAAG A UCCUGAAC	76	GTTCAGGA GGCTAGCTACAACGA CTTTTAAT	1778
348	GAUCCUGA A CUGAGUUU	77	AAACTCAG GGCTAGCTACAACGA TCAGGATC	1779
353	UGAACUGA G UUUAAAAG	78	CTTTTAAA GGCTAGCTACAACGA TCAGTTCA	1780
362	UUUAAAAG G CACCCAGC	79	GCTGGGTG GGCTAGCTACAACGA CTTTTAAA	1781
364	UAAAAGGC A CCCAGCAC	80	GTGCTGGG GGCTAGCTACAACGA GCCTTTTA	1782
369	GGCACCCA G CACAUCAU	81	ATGATGTG GGCTAGCTACAACGA TGGGTGCC	1783
371	CACCCAGC A CAUCAUGC	82	GCATGATG GGCTAGCTACAACGA GCTGGGTG	1784
373	CCCAGCAC A UCAUGCAA	83	TTGCATGA GGCTAGCTACAACGA GTGCTGGG	1785
376	AGCACAUC A UGCAAGCA	84	TGCTTGCA GGCTAGCTACAACGA GATGTGCT	1786
378	CACAUCAU G CAAGCAGG	85	CCTGCTTG GGCTAGCTACAACGA ATGATGTG	1787
382	UCAUGCAA G CAGGCCAG	86	CTGGCCTG GGCTAGCTACAACGA TTGCATGA	1788
386	GCAAGCAG G CCAGACAC	87	GTGTCTGG GGCTAGCTACAACGA CTGCTTGC	1789
391	CAGGCCAG A CACUGCAU	88	ATGCAGTG GGCTAGCTACAACGA CTGGCCTG	1790
393	GGCCAGAC A CUGCAUCU	89	AGATGCAG GGCTAGCTACAACGA GTCTGGCC	1791
396	CAGACACU G CAUCUCCA	90	TGGAGATG GGCTAGCTACAACGA AGTGTCTG	1792
398	GACACUGC A UCUCCAAU	91	ATTGGAGA GGCTAGCTACAACGA GCAGTGTC	1793
405	CAUCUCCA A UGCAGGGG	92	CCCCTGCA GGCTAGCTACAACGA TGGAGATG	1794
407	UCUCCAAU G CAGGGGGG	93	CCCCCCTG GGCTAGCTACAACGA ATTGGAGA	1795
418	GGGGGGAA G CAGCCCAU	94	ATGGGCTG GGCTAGCTACAACGA TTCCCCCC	1796
421	GGGAAGCA G CCCAUAAA	95	TTTATGGG GGCTAGCTACAACGA TGCTTCCC	1797
425	AGCAGCCC A UAAAUGGU	96	ACCATTTA GGCTAGCTACAACGA GGGCTGCT	1798
429	GCCCAUAA A UGGUCUUU	97	AAAGACCA GGCTAGCTACAACGA TTATGGGC	1799
432	CAUAAAUG G UCUUUGCC	98	GGCAAAGA GGCTAGCTACAACGA CATTTATG	1800
438	UGGUCUUU G CCUGAAAU	99	ATTTCAGG GGCTAGCTACAACGA AAAGACCA	1801
445	UGCCUGAA A UGGUGAGU	100	ACTCACCA GGCTAGCTACAACGA TTCAGGCA	1802

448	CUGAAAUG G UGAGUAAG	101	CTTACTCA GGCTAGCTACAACGA CATTTCAG	1803
452	AAUGGUGA G UAAGGAAA	102	TTTCCTTA GGCTAGCTACAACGA TCACCATT	1804
461	UAAGGAAA G CGAAAGGC	103	GCCTTTCG GGCTAGCTACAACGA TTTCCTTA	1805
468	AGCGAAAG G CUGAGCAU	104	ATGCTCAG GGCTAGCTACAACGA CTTTCGCT	1806
473	AAGGCUGA G CAUAACUA	105	TAGTTATG GGCTAGCTACAACGA TCAGCCTT	1807
475	GGCUGAGC A UAACUAAA	106	TTTAGTTA GGCTAGCTACAACGA GCTCAGCC	1808
478	UGAGCAUA A CUAAAUCU	107	AGATTTAG GGCTAGCTACAACGA TATGCTCA	1809
483	AUAACUAA A UCUGCCUG	108	CAGGCAGA GGCTAGCTACAACGA TTAGTTAT	1810
487	CUAAAUCU G CCUGUGGA	109	TCCACAGG GGCTAGCTACAACGA AGATTTAG	1811
491	AUCUGCCU G UGGAAGAA	110	TTCTTCCA GGCTAGCTACAACGA AGGCAGAT	1812
500	UGGAAGAA A UGGCAAAC	111	GTTTGCCA GGCTAGCTACAACGA TTCTTCCA	1813
503	AAGAAAUG G CAAACAAU	112	ATTGTTTG GGCTAGCTACAACGA CATTTCTT	1814
507	AAUGGCAA A CAAUUCUG	113	CAGAATTG GGCTAGCTACAACGA TTGCCATT	1815
510	GGCAAACA A UUCUGCAG	114	CTGCAGAA GGCTAGCTACAACGA TGTTTGCC	1816
515	ACAAUUCU G CAGUACUU	115	AAGTACTG GGCTAGCTACAACGA AGAATTGT	1817
518	AUUCUGCA G UACUUUAA	116	TTAAAGTA GGCTAGCTACAACGA TGCAGAAT	1818
520	UCUGCAGU A CUUUAACC	117	GGTTAAAG GGCTAGCTACAACGA ACTGCAGA	1819
526	GUACUUUA A CCUUGAAC	118	GTTCAAGG GGCTAGCTACAACGA TAAAGTAC	1820
533	AACCUUGA A CACAGCUC	119	GAGCTGTG GGCTAGCTACAACGA TCAAGGTT	1821
535	CCUUGAAC A CAGCUCAA	120	TTGAGCTG GGCTAGCTACAACGA GTTCAAGG	1822
538	UGAACACA G CUCAAGCA	121	TGCTTGAG GGCTAGCTACAACGA TGTGTTCA	1823
544	CAGCUCAA G CAAACCAC	122	GTGGTTTG GGCTAGCTACAACGA TTGAGCTG	1824
548	UCAAGCAA A CCACACUG	123	CAGTGTGG GGCTAGCTACAACGA TTGCTTGA	1825
551	AGCAAACC A CACUGGCU	124	AGCCAGTG GGCTAGCTACAACGA GGTTTGCT	1826
553	CAAACCAC A CUGGCUUC	125	GAAGCCAG GGCTAGCTACAACGA GTGGTTTG	1827
557	CCACACUG G CUUCUACA	126	TGTAGAAG GGCTAGCTACAACGA CAGTGTGG	1828
563	UGGCUUCU A CAGCUGCA	127	TGCAGCTG GGCTAGCTACAACGA AGAAGCCA	1829
566	CUUCUACA G CUGCAAAU	128	ATTTGCAG GGCTAGCTACAACGA TGTAGAAG	1830
569	CUACAGCU G CAAAUAUC	129	GATATTTG GGCTAGCTACAACGA AGCTGTAG	1831
573	AGCUGCAA A UAUCUAGC	130	GCTAGATA GGCTAGCTACAACGA TTGCAGCT	1832
575	CUGCAAAU A UCUAGCUG	131	CAGCTAGA GGCTAGCTACAACGA ATTTGCAG	1833
580	AAUAUCUA G CUGUACCU	132	AGGTACAG GGCTAGCTACAACGA TAGATATT	1834
583	AUCUAGCU G UACCUACU	133	AGTAGGTA GGCTAGCTACAACGA AGCTAGAT	1835
585	CUAGCUGU A CCUACUUC	134	GAAGTAGG GGCTAGCTACAACGA ACAGCTAG	1836
589	CUGUACCU A CUUCAAAG	135	CTTTGAAG GGCTAGCTACAACGA AGGTACAG	1837
607	AGAAGGAA A CAGAAUCU	136	AGATTCTG GGCTAGCTACAACGA TTCCTTCT	1838
612	GAAACAGA A UCUGCAAU	137	ATTGCAGA GGCTAGCTACAACGA TCTGTTTC	1839
616	CAGAAUCU G CAAUCUAU	138	ATAGATTG GGCTAGCTACAACGA AGATTCTG	1840
619	AAUCUGCA A UCUAUAUA	139	TATATAGA GGCTAGCTACAACGA TGCAGATT	1841
623	UGCAAUCU A UAUAUUUA	140	TAAATATA GGCTAGCTACAACGA AGATTGCA	1842
625	CAAUCUAU A UAUUUAUU	141	AATAAATA GGCTAGCTACAACGA ATAGATTG	1843
627	AUCUAUAU A UUUAUUAG	142	CTAATAAA GGCTAGCTACAACGA ATATAGAT	1844
631	AUAUAUUU A UUAGUGAU	143	ATCACTAA GGCTAGCTACAACGA AAATATAT	1845
635	AUUUAUUA G UGAUACAG	144	CTGTATCA GGCTAGCTACAACGA TAATAAAT	1846
638	UAUUAGUG A UACAGGUA	145	TACCTGTA GGCTAGCTACAACGA CACTAATA	1847
640	UUAGUGAU A CAGGUAGA	146	TCTACCTG GGCTAGCTACAACGA ATCACTAA	1848
644	UGAUACAG G UAGACCUU	147	AAGGTCTA GGCTAGCTACAACGA CTGTATCA	1849
648	ACAGGUAG A CCUUUCGU	148	ACGAAAGG GGCTAGCTACAACGA CTACCTGT	1850
655	GACCUUUC G UAGAGAUG	149	CATCTCTA GGCTAGCTACAACGA GAAAGGTC	1851
661	UCGUAGAG A UGUACAGU	150	ACTGTACA GGCTAGCTACAACGA CTCTACGA	1852
663	GUAGAGAU G UACAGUGA	151	TCACTGTA GGCTAGCTACAACGA ATCTCTAC	1853
665	AGAGAUGU A CAGUGAAA	152	TTTCACTG GGCTAGCTACAACGA ACATCTCT	1854

668	GAUGUACA G UGAAAUCC	153	GGATTTCA GGCTAGCTACAACGA TGTACATC	1855
673	ACAGUGAA A UCCCCGAA	154	TTCGGGGA GGCTAGCTACAACGA TTCACTGT	1856
682	UCCCCGAA A UUAUACAC	155	GTGTATAA GGCTAGCTACAACGA TTCGGGGA	1857
685	CCGAAAUU A UACACAUG	156	CATGTGTA GGCTAGCTACAACGA AATTTCGG	1858
687	GAAAUUAU A CACAUGAC	157	GTCATGTG GGCTAGCTACAACGA ATAATTTC	1859
689	AAUUAUAC A CAUGACUG	158	CAGTCATG GGCTAGCTACAACGA GTATAATT	1860
691	UUAUACAC A UGACUGAA	159	TTCAGTCA GGCTAGCTACAACGA GTGTATAA	1861
694	UACACAUG A CUGAAGGA	160	TCCTTCAG GGCTAGCTACAACGA CATGTGTA	1862
708	GGAAGGGA G CUCGUCAU	161	ATGACGAG GGCTAGCTACAACGA TCCCTTCC	1863
712	GGGAGCUC G UCAUUCCC	162	GGGAATGA GGCTAGCTACAACGA GAGCTCCC	1864
715	AGCUCGUC A UUCCCUGC	163	GCAGGGAA GGCTAGCTACAACGA GACGAGCT	1865
722	CAUUCCCU G CCGGGUUA	164	TAACCCGG GGCTAGCTACAACGA AGGGAATG	1866
727	CCUGCCGG G UUACGUCA	165	TGACGTAA GGCTAGCTACAACGA CCGGCAGG	1867
730	GCCGGGUU A CGUCACCU	166	AGGTGACG GGCTAGCTACAACGA AACCCGGC	1868
732	CGGGUUAC G UCACCUAA	167	TTAGGTGA GGCTAGCTACAACGA GTAACCCG	1869
735	GUUACGUC A CCUAACAU	168	ATGTTAGG GGCTAGCTACAACGA GACGTAAC	1870
740	GUCACCUA A CAUCACUG	169	CAGTGATG GGCTAGCTACAACGA TAGGTGAC	1871
742	CACCUAAC A UCACUGUU	170	AACAGTGA GGCTAGCTACAACGA GTTAGGTG	1872
745	CUAACAUC A CUGUUACU	171	AGTAACAG GGCTAGCTACAACGA GATGTTAG	1873
748	ACAUCACU G UUACUUUA	172	TAAAGTAA GGCTAGCTACAACGA AGTGATGT	1874
751	UCACUGUU A CUUUAAAA	173	TTTTAAAG GGCTAGCTACAACGA AACAGTGA	1875
762	UUAAAAAA G UUUCCACU	174	AGTGGAAA GGCTAGCTACAACGA TTTTTTAA	1876
768	AAGUUUCC A CUUGACAC	175	GTGTCAAG GGCTAGCTACAACGA GGAAACTT	1877
773	UCCACUUG A CACUUUGA	176	TCAAAGTG GGCTAGCTACAACGA CAAGTGGA	1878
775	CACUUGAC A CUUUGAUC	177	GATCAAAG GGCTAGCTACAACGA GTCAAGTG	1879
781	ACACUUUG A UCCCUGAU	178	ATCAGGGA GGCTAGCTACAACGA CAAAGTGT	1880
788	GAUCCCUG A UGGAAAAC	179	GTTTTCCA GGCTAGCTACAACGA CAGGGATC	1881
795	GAUGGAAA A CGCAUAAU	180	ATTATGCG GGCTAGCTACAACGA TTTCCATC	1882
797	UGGAAAAC G CAUAAUCU	181	AGATTATG GGCTAGCTACAACGA GTTTTCCA	1883
799	GAAAACGC A UAAUCUGG	182	CCAGATTA GGCTAGCTACAACGA GCGTTTTC	1884
802	AACGCAUA A UCUGGGAC	183	GTCCCAGA GGCTAGCTACAACGA TATGCGTT	1885
809	AAUCUGGG A CAGUAGAA	184	TTCTACTG GGCTAGCTACAACGA CCCAGATT	1886
812	CUGGGACA G UAGAAAGG	185	CCTTTCTA GGCTAGCTACAACGA TGTCCCAG	1887
821	UAGAAAGG G CUUCAUCA	186	TGATGAAG GGCTAGCTACAACGA CCTTTCTA	1888
826	AGGGCUUC A UCAUAUCA	187	TGATATGA GGCTAGCTACAACGA GAAGCCCT	1889
829	GCUUCAUC A UAUCAAAU	188	ATTTGATA GGCTAGCTACAACGA GATGAAGC	1890
831	UUCAUCAU A UCAAAUGC	189	GCATTTGA GGCTAGCTACAACGA ATGATGAA	1891
836	CAUAUCAA A UGCAACGU	190	ACGTTGCA GGCTAGCTACAACGA TTGATATG	1892
838	UAUCAAAU G CAACGUAC	191	GTACGTTG GGCTAGCTACAACGA ATTTGATA	1893
841	CAAAUGCA A CGUACAAA	192	TTTGTACG GGCTAGCTACAACGA TGCATTTG	1894
843	AAUGCAAC G UACAAAGA	193	TCTTTGTA GGCTAGCTACAACGA GTTGCATT	1895
845	UGCAACGU A CAAAGAAA	194	TTTCTTTG GGCTAGCTACAACGA ACGTTGCA	1896
853	ACAAAGAA A UAGGGCUU	195	AAGCCCTA GGCTAGCTACAACGA TTCTTTGT	1897
858	GAAAUAGG G CUUCUGAC	196	GTCAGAAG GGCTAGCTACAACGA CCTATTTC	1898
865	GGCUUCUG A CCUGUGAA	197	TTCACAGG GGCTAGCTACAACGA CAGAAGCC	1899
869	UCUGACCU G UGAAGCAA	198	TTGCTTCA GGCTAGCTACAACGA AGGTCAGA	1900
874	CCUGUGAA G CAACAGUC	199	GACTGTTG GGCTAGCTACAACGA TTCACAGG	1901
877	GUGAAGCA A CAGUCAAU	200	ATTGACTG GGCTAGCTACAACGA TGCTTCAC	1902
880	AAGCAACA G UCAAUGGG	201	CCCATTGA GGCTAGCTACAACGA TGTTGCTT	1903
884	AACAGUCA A UGGGCAUU	202	AATGCCCA GGCTAGCTACAACGA TGACTGTT	1904
888	GUCAAUGG G CAUUUGUA	203	TACAAATG GGCTAGCTACAACGA CCATTGAC	1905
890	CAAUGGGC A UUUGUAUA	204	TATACAAA GGCTAGCTACAACGA GCCCATTG	1906

894	GGGCAUUU G UAUAAGAC	205	GTCTTATA GGCTAGCTACAACGA AAATGCCC	1907
896	GCAUUUGU A UAAGACAA	206	TTGTCTTA GGCTAGCTACAACGA ACAAATGC	1908
901	UGUAUAAG A CAAACUAU	207	ATAGTTTG GGCTAGCTACAACGA CTTATACA	1909
905	UAAGACAA A CUAUCUCA	208	TGAGATAG GGCTAGCTACAACGA TTGTCTTA	1910
908	GACAAACU A UCUCACAC	209	GTGTGAGA GGCTAGCTACAACGA AGTTTGTC	1911
913	ACUAUCUC A CACAUCGA	210	TCGATGTG GGCTAGCTACAACGA GAGATAGT	1912
915	UAUCUCAC A CAUCGACA	211	TGTCGATG GGCTAGCTACAACGA GTGAGATA	1913
917	UCUCACAC A UCGACAAA	212	TTTGTCGA GGCTAGCTACAACGA GTGTGAGA	1914
921	ACACAUCG A CAAACCAA	213	TTGGTTTG GGCTAGCTACAACGA CGATGTGT	1915
925	AUCGACAA A CCAAUACA	214	TGTATTGG GGCTAGCTACAACGA TTGTCGAT	1916
929	ACAAACCA A UACAAUCA	215	TGATTGTA GGCTAGCTACAACGA TGGTTTGT	1917
931	AAACCAAU A CAAUCAUA	216	TATGATTG GGCTAGCTACAACGA ATTGGTTT	1918
934	CCAAUACA A UCAUAGAU	217	ATCTATGA GGCTAGCTACAACGA TGTATTGG	1919
937	AUACAAUC A UAGAUGUC	218	GACATCTA GGCTAGCTACAACGA GATTGTAT	1920
941	AAUCAUAG A UGUCCAAA	219	TTTGGACA GGCTAGCTACAACGA CTATGATT	1921
943	UCAUAGAU G UCCAAAUA	220	TATTTGGA GGCTAGCTACAACGA ATCTATGA	1922
949	AUGUCCAA A UAAGCACA	221	TGTGCTTA GGCTAGCTACAACGA TTGGACAT	1923
953	CCAAAUAA G CACACCAC	222	GTGGTGTG GGCTAGCTACAACGA TTATTTGG	1924
955	AAAUAAGC A CACCACGC	223	GCGTGGTG GGCTAGCTACAACGA GCTTATTT	1925
957	AUAAGCAC A CCACGCCC	224	GGGCGTGG GGCTAGCTACAACGA GTGCTTAT	1926
960	AGCACACC A CGCCCAGU	225	ACTGGGCG GGCTAGCTACAACGA GGTGTGCT	1927
962	CACACCAC G CCCAGUCA	226	TGACTGGG GGCTAGCTACAACGA GTGGTGTG	1928
967	CACGCCCA G UCAAAUUA	227	TAATTTGA GGCTAGCTACAACGA TGGGCGTG	1929
972	CCAGUCAA A UUACUUAG	228	CTAAGTAA GGCTAGCTACAACGA TTGACTGG	1930
975	GUCAAAUU A CUUAGAGG	229	CCTCTAAG GGCTAGCTACAACGA AATTTGAC	1931
983	ACUUAGAG G CCAUACUC	230	GAGTATGG GGCTAGCTACAACGA CTCTAAGT	1932
986	UAGAGGCC A UACUCUUG	231	CAAGAGTA GGCTAGCTACAACGA GGCCTCTA	1933
988	GAGGCCAU A CUCUUGUC	232	GACAAGAG GGCTAGCTACAACGA ATGGCCTC	1934
994	AUACUCUU G UCCUCAAU	233	ATTGAGGA GGCTAGCTACAACGA AAGAGTAT	1935
1001	UGUCCUCA A UUGUACUG	234	CAGTACAA GGCTAGCTACAACGA TGAGGACA	1936
1004	CCUCAAUU G UACUGCUA	235	TAGCAGTA GGCTAGCTACAACGA AATTGAGG	1937
1006	UCAAUUGU A CUGCUACC	236	GGTAGCAG GGCTAGCTACAACGA ACAATTGA	1938
1009	AUUGUACU G CUACCACU	237	AGTGGTAG GGCTAGCTACAACGA AGTACAAT	1939
1012	GUACUGCU A CCACUCCC	238	GGGAGTGG GGCTAGCTACAACGA AGCAGTAC	1940
1015	CUGCUACC A CUCCCUUG	239	CAAGGGAG GGCTAGCTACAACGA GGTAGCAG	1941
1025	UCCCUUGA A CACGAGAG	240	CTCTCGTG GGCTAGCTACAACGA TCAAGGGA	1942
1027	CCUUGAAC A CGAGAGUU	241	AACTCTCG GGCTAGCTACAACGA GTTCAAGG	1943
1033	ACACGAGA G UUCAAAUG	242	CATTTGAA GGCTAGCTACAACGA TCTCGTGT	1944
1039	GAGUUCAA A UGACCUGG	243	CCAGGTCA GGCTAGCTACAACGA TTGAACTC	1945
1042	UUCAAAUG A CCUGGAGU	244	ACTCCAGG GGCTAGCTACAACGA CATTTGAA	1946
1049	GACCUGGA G UUACCCUG	245	CAGGGTAA GGCTAGCTACAACGA TCCAGGTC	1947
1052	CUGGAGUU A CCCUGAUG	246	CATCAGGG GGCTAGCTACAACGA AACTCCAG	1948
1058	UUACCCUG A UGAAAAAA	247	TTTTTCA GGCTAGCTACAACGA CAGGGTAA	1949
1067	UGAAAAAA A UAAGAGAG	248	CTCTCTTA GGCTAGCTACAACGA TTTTTTCA	1950
1075	AUAAGAGA G CUUCCGUA	249	TACGGAAG GGCTAGCTACAACGA TCTCTTAT	1951
1081	GAGCUUCC G UAAGGCGA	250	TCGCCTTA GGCTAGCTACAACGA GGAAGCTC	1952
1086	UCCGUAAG G CGACGAAU	251	ATTCGTCG GGCTAGCTACAACGA CTTACGGA	1953
1089	GUAAGGCG A CGAAUUGA	252	TCAATTCG GGCTAGCTACAACGA CGCCTTAC	1954
1093	GGCGACGA A UUGACCAA	253	TTGGTCAA GGCTAGCTACAACGA TCGTCGCC	1955
1097	ACGAAUUG A CCAAAGCA	254	TGCTTTGG GGCTAGCTACAACGA CAATTCGT	1956
1103	UGACCAAA G CAAUUCCC	255	GGGAATTG GGCTAGCTACAACGA TTTGGTCA	1957
1106	CCAAAGCA A UUCCCAUG	256	CATGGGAA GGCTAGCTACAACGA TGCTTTGG	1958

1112	CAAUUCCC A UGCCAACA	257	TGTTGGCA GGCTAGCTACAACGA GGGAATTG	1959
1114	AUUCCCAU G CCAACAUA	258	TATGTTGG GGCTAGCTACAACGA ATGGGAAT	1960
1118	CCAUGCCA A CAUAUUCU	259	AGAATATG GGCTAGCTACAACGA TGGCATGG	1961
1120	AUGCCAAC A UAUUCUAC	260	GTAGAATA GGCTAGCTACAACGA GTTGGCAT	1962
1122	GCCAACAU A UUCUACAG	261	CTGTAGAA GGCTAGCTACAACGA ATGTTGGC	1963
1127	CAUAUUCU A CAGUGUUC	262	GAACACTG GGCTAGCTACAACGA AGAATATG	1964
1130	AUUCUACA G UGUUCUUA	263	TAAGAACA GGCTAGCTACAACGA TGTAGAAT	1965
1132	UCUACAGU G UUCUUACU	264	AGTAAGAA GGCTAGCTACAACGA ACTGTAGA	1966
1138	GUGUUCUU A CUAUUGAC	265	GTCAATAG GGCTAGCTACAACGA AAGAACAC	1967
1141	UUCUUACU A UUGACAAA	266	TTTGTCAA GGCTAGCTACAACGA AGTAAGAA	1968
1145	UACUAUUG A CAAAAUGC	267	GCATTTTG GGCTAGCTACAACGA CAATAGTA	1969
1150	UUGACAAA A UGCAGAAC	268	GTTCTGCA GGCTAGCTACAACGA TTTGTCAA	1970
1152	GACAAAAU G CAGAACAA	269	TTGTTCTG GGCTAGCTACAACGA ATTTTGTC	1971
1157	AAUGCAGA A CAAAGACA	270	TGTCTTTG GGCTAGCTACAACGA TCTGCATT	1972
1163	GAACAAAG A CAAAGGAC	271	GTCCTTTG GGCTAGCTACAACGA CTTTGTTC	1973
1170	GACAAAGG A CUUUAUAC	272	GTATAAAG GGCTAGCTACAACGA CCTTTGTC	1974
1175	AGGACUUU A UACUUGUC	273	GACAAGTA GGCTAGCTACAACGA AAAGTCCT	1975
1177	GACUUUAU A CUUGUCGU	274	ACGACAAG GGCTAGCTACAACGA ATAAAGTC	1976
1181	UUAUACUU G UCGUGUAA	275	TTACACGA GGCTAGCTACAACGA AAGTATAA	1977
1184	UACUUGUC G UGUAAGGA	276	TCCTTACA GGCTAGCTACAACGA GACAAGTA	1978
1186	CUUGUCGU G UAAGGAGU	277	ACTCCTTA GGCTAGCTACAACGA ACGACAAG	1979
1193	UGUAAGGA G UGGACCAU	278	ATGGTCCA GGCTAGCTACAACGA TCCTTACA	1980
1197	AGGAGUGG A CCAUCAUU	279	AATGATGG GGCTAGCTACAACGA CCACTCCT	1981
1200	AGUGGACC A UCAUUCAA	280	TTGAATGA GGCTAGCTACAACGA GGTCCACT	1982
1203	GGACCAUC A UUCAAAUC	281	GATTTGAA GGCTAGCTACAACGA GATGGTCC	1983
1209	UCAUUCAA A UCUGUUAA	282	TTAACAGA GGCTAGCTACAACGA TTGAATGA	1984
1213	UCAAAUCU G UUAACACC	283	GGTGTTAA GGCTAGCTACAACGA AGATTTGA	1985
1217	AUCUGUUA A CACCUCAG	284	CTGAGGTG GGCTAGCTACAACGA TAACAGAT	1986
1219	CUGUUAAC A CCUCAGUG	285	CACTGAGG GGCTAGCTACAACGA GTTAACAG	1987
1225	ACACCUCA G UGCAUAUA	286	TATATGCA GGCTAGCTACAACGA TGAGGTGT	1988
1227	ACCUCAGU G CAUAUAUA	287	TATATATG GGCTAGCTACAACGA ACTGAGGT	1989
1229	CUCAGUGC A UAUAUAUG	288	CATATATA GGCTAGCTACAACGA GCACTGAG	1990
1231	CAGUGCAU A UAUAUGAU	289	ATCATATA GGCTAGCTACAACGA ATGCACTG	1991
1233	GUGCAUAU A UAUGAUAA	290	TTATCATA GGCTAGCTACAACGA ATATGCAC	1992
1235	GCAUAUAU A UGAUAAAG	291	CTTTATCA GGCTAGCTACAACGA ATATATGC	1993
1238	UAUAUAUG A UAAAGCAU	292	ATGCTTTA GGCTAGCTACAACGA CATATATA	1994
1243	AUGAUAAA G CAUUCAUC	293	GATGAATG GGCTAGCTACAACGA TTTATCAT	1995
1245	GAUAAAGC A UUCAUCAC	294	GTGATGAA GGCTAGCTACAACGA GCTTTATC	1996
1249	AAGCAUUC A UCACUGUG	295	CACAGTGA GGCTAGCTACAACGA GAATGCTT	1997
1252	CAUUCAUC A CUGUGAAA	296	TTTCACAG GGCTAGCTACAACGA GATGAATG	1998
1255	UCAUCACU G UGAAACAU	297	ATGTTTCA GGCTAGCTACAACGA AGTGATGA	1999
1260	ACUGUGAA A CAUCGAAA	298	TTTCGATG GGCTAGCTACAACGA TTCACAGT	2000
1262	UGUGAAAC A UCGAAAAC	299	GTTTTCGA GGCTAGCTACAACGA GTTTCACA	2001
1269	CAUCGAAA A CAGCAGGU	300	ACCTGCTG GGCTAGCTACAACGA TTTCGATG	2002
1272	CGAAAACA G CAGGUGCU	301	AGCACCTG GGCTAGCTACAACGA TGTTTTCG	2003
1276	AACAGCAG G UGCUUGAA	302	TTCAAGCA GGCTAGCTACAACGA CTGCTGTT	2004
1278	CAGCAGGU G CUUGAAAC	303	GTTTCAAG GGCTAGCTACAACGA ACCTGCTG	2005
1285	UGCUUGAA A CCGUAGCU	304	AGCTACGG GGCTAGCTACAACGA TTCAAGCA	2006
1288	UUGAAACC G UAGCUGGC	305	GCCAGCTA GGCTAGCTACAACGA GGTTTCAA	2007
1291	AAACCGUA G CUGGCAAG	306	CTTGCCAG GGCTAGCTACAACGA TACGGTTT	2008
1295	CGUAGCUG G CAAGCGGU	307	ACCGCTTG GGCTAGCTACAACGA CAGCTACG	2009
1299	GCUGGCAA G CGGUCUUA	308	TAAGACCG GGCTAGCTACAACGA TTGCCAGC	2010

1302	GGCAAGCG G UCUUACCG	309	CGGTAAGA GGCTAGCTACAACGA CGCTTGCC	2011
1307	GCGGUCUU A CCGGCUCU	310	AGAGCCGG GGCTAGCTACAACGA AAGACCGC	2012
1311	UCUUACCG G CUCUCUAU	311	ATAGAGAG GGCTAGCTACAACGA CGGTAAGA	2013
1318	GGCUCUCU A UGAAAGUG	312	CACTTTCA GGCTAGCTACAACGA AGAGAGCC	2014
1324	CUAUGAAA G UGAAGGCA	313	TGCCTTCA GGCTAGCTACAACGA TTTCATAG	2015
1330	AAGUGAAG G CAUUUCCC	314	GGGAAATG GGCTAGCTACAACGA CTTCACTT	2016
1332	GUGAAGGC A UUUCCCUC	315	GAGGGAAA GGCTAGCTACAACGA GCCTTCAC	2017
1341	UUUCCCUC G CCGGAAGU	316	ACTTCCGG GGCTAGCTACAACGA GAGGGAAA	2018
1348	CGCCGGAA G UUGUAUGG	317	CCATACAA GGCTAGCTACAACGA TTCCGGCG	2019
1351	CGGAAGUU G UAUGGUUA	318	TAACCATA GGCTAGCTACAACGA AACTTCCG	2020
1353	GAAGUUGU A UGGUUAAA	319	TTTAACCA GGCTAGCTACAACGA ACAACTTC	2021
1356	GUUGUAUG G UUAAAAGA	320	TCTTTTAA GGCTAGCTACAACGA CATACAAC	2022
1364	GUUAAAAG A UGGGUUAC	321	GTAACCCA GGCTAGCTACAACGA CTTTTAAC	2023
1368	AAAGAUGG G UUACCUGC	322	GCAGGTAA GGCTAGCTACAACGA CCATCTTT	2024
1371	GAUGGGUU A CCUGCGAC	323	GTCGCAGG GGCTAGCTACAACGA AACCCATC	2025
1375	GGUUACCU G CGACUGAG	324	CTCAGTCG GGCTAGCTACAACGA AGGTAACC	2026
1378	UACCUGCG A CUGAGAAA	325	TTTCTCAG GGCTAGCTACAACGA CGCAGGTA	2027
1386	ACUGAGAA A UCUGCUCG	326	CGAGCAGA GGCTAGCTACAACGA TTCTCAGT	2028
1390	AGAAAUCU G CUCGCUAU	327	ATAGCGAG GGCTAGCTACAACGA AGATTTCT	2029
1394	AUCUGCUC G CUAUUUGA	328	TCAAATAG GGCTAGCTACAACGA GAGCAGAT	2030
1397	UGCUCGCU A UUUGACUC	329	GAGTCAAA GGCTAGCTACAACGA AGCGAGCA	2031
1402	GCUAUUUG A CUCGUGGC	330	GCCACGAG GGCTAGCTACAACGA CAAATAGC	2032
1406	UUUGACUC G UGGCUACU	331	AGTAGCCA GGCTAGCTACAACGA GAGTCAAA	2033
1409	GACUCGUG G CUACUCGU	332	ACGAGTAG GGCTAGCTACAACGA CACGAGTC	2034
1412	UCGUGGCU A CUCGUUAA	333	TTAACGAG GGCTAGCTACAACGA AGCCACGA	2035
1416	GGCUACUC G UUAAUUAU	334	ATAATTAA GGCTAGCTACAACGA GAGTAGCC	2036
1420	ACUCGUUA A UUAUCAAG	335	CTTGATAA GGCTAGCTACAACGA TAACGAGT	2037
1423	CGUUAAUU A UCAAGGAC	336	GTCCTTGA GGCTAGCTACAACGA AATTAACG	2038
1430	UAUCAAGG A CGUAACUG	337	CAGTTACG GGCTAGCTACAACGA CCTTGATA	2039
1432	UCAAGGAC G UAACUGAA	338	TTCAGTTA GGCTAGCTACAACGA GTCCTTGA	2040
1435	AGGACGUA A CUGAAGAG	339	CTCTTCAG GGCTAGCTACAACGA TACGTCCT	2041
1445	UGAAGAGG A UGCAGGGA	340	TCCCTGCA GGCTAGCTACAACGA CCTCTTCA	2042
1447	AAGAGGAU G CAGGGAAU	341	ATTCCCTG GGCTAGCTACAACGA ATCCTCTT	2043
1454	UGCAGGGA A UUAUACAA	342	TTGTATAA GGCTAGCTACAACGA TCCCTGCA	2044
1457	AGGGAAUU A UACAAUCU	343	AGATTGTA GGCTAGCTACAACGA AATTCCCT	2045
1459	GGAAUUAU A CAAUCUUG	344	CAAGATTG GGCTAGCTACAACGA ATAATTCC	2046
1462	AUUAUACA A UCUUGCUG	345	CAGCAAGA GGCTAGCTACAACGA TGTATAAT	2047
1467	ACAAUCUU G CUGAGCAU	346	ATGCTCAG GGCTAGCTACAACGA AAGATTGT	2048
1472	CUUGCUGA G CAUAAAAC	347	GTTTTATG GGCTAGCTACAACGA TCAGCAAG	2049
1474	UGCUGAGC A UAAAACAG	348	CTGTTTTA GGCTAGCTACAACGA GCTCAGCA	2050
1479	AGCAUAAA A CAGUCAAA	349	TTTGACTG GGCTAGCTACAACGA TTTATGCT	2051
1482	AUAAAACA G UCAAAUGU	350	ACATTTGA GGCTAGCTACAACGA TGTTTTAT	2052
1487	ACAGUCAA A UGUGUUUA	351	TAAACACA GGCTAGCTACAACGA TTGACTGT	2053
1489	AGUCAAAU G UGUUUAAA	352	TTTAAACA GGCTAGCTACAACGA ATTTGACT	2054
1491	UCAAAUGU G UUUAAAAA	353	TTTTTAAA GGCTAGCTACAACGA ACATTTGA	2055
1499	GUUUAAAA A CCUCACUG	354	CAGTGAGG GGCTAGCTACAACGA TTTTAAAC	2056
1504	AAAACCUC A CUGCCACU	355	AGTGGCAG GGCTAGCTACAACGA GAGGTTTT	2057
1507	ACCUCACU G CCACUCUA	356	TAGAGTGG GGCTAGCTACAACGA AGTGAGGT	2058
1510	UCACUGCC A CUCUAAUU	357	AATTAGAG GGCTAGCTACAACGA GGCAGTGA	2059
1516	CCACUCUA A UUGUCAAU	358	ATTGACAA GGCTAGCTACAACGA TAGAGTGG	2060
1519	CUCUAAUU G UCAAUGUG	359	CACATTGA GGCTAGCTACAACGA AATTAGAG	2061
1523	AAUUGUCA A UGUGAAAC	360	GTTTCACA GGCTAGCTACAACGA TGACAATT	2062

1525	UUGUCAAU G UGAAACCC	361	GGGTTTCA GGCTAGCTACAACGA ATTGACAA	2063
1530	AAUGUGAA A CCCCAGAU	362	ATCTGGGG GGCTAGCTACAACGA TTCACATT	2064
1537	AACCCCAG A UUUACGAA	363	TTCGTAAA GGCTAGCTACAACGA CTGGGGTT	2065
1541	CCAGAUUU A CGAAAAGG	364	CCTTTTCG GGCTAGCTACAACGA AAATCTGG	2066
1549	ACGAAAAG G CCGUGUCA	365	TGACACGG GGCTAGCTACAACGA CTTTTCGT	2067
1552	AAAAGGCC G UGUCAUCG	366	CGATGACA GGCTAGCTACAACGA GGCCTTTT	2068
1554	AAGGCCGU G UCAUCGUU	367	AACGATGA GGCTAGCTACAACGA ACGGCCTT	2069
1557	GCCGUGUC A UCGUUUCC	368	GGAAACGA GGCTAGCTACAACGA GACACGGC	2070
1560	GUGUCAUC G UUUCCAGA	369	TCTGGAAA GGCTAGCTACAACGA GATGACAC	2071
1568	GUUUCCAG A CCCGGCUC	370	GAGCCGGG GGCTAGCTACAACGA CTGGAAAC	2072
1573	CAGACCCG G CUCUCUAC	371	GTAGAGAG GGCTAGCTACAACGA CGGGTCTG	2073
1580	GGCUCUCU A CCCACUGG	372	CCAGTGGG GGCTAGCTACAACGA AGAGAGCC	2074
1584	CUCUACCC A CUGGGCAG	373	CTGCCCAG GGCTAGCTACAACGA GGGTAGAG	2075
1589	CCCACUGG G CAGCAGAC	374	GTCTGCTG GGCTAGCTACAACGA CCAGTGGG	2076
1592	ACUGGGCA G CAGACAAA	375	TTTGTCTG GGCTAGCTACAACGA TGCCCAGT	2077
1596	GGCAGCAG A CAAAUCCU	376	AGGATTTG GGCTAGCTACAACGA CTGCTGCC	2078
1600	GCAGACAA A UCCUGACU	377	AGTCAGGA GGCTAGCTACAACGA TTGTCTGC	2079
1606	AAAUCCUG A CUUGUACC	378	GGTACAAG GGCTAGCTACAACGA CAGGATTT	2080
1610	CCUGACUU G UACCGCAU	379	ATGCGGTA GGCTAGCTACAACGA AAGTCAGG	2081
1612	UGACUUGU A CCGCAUAU	380	ATATGCGG GGCTAGCTACAACGA ACAAGTCA	2082
1615	CUUGUACC G CAUAUGGU	381	ACCATATG GGCTAGCTACAACGA GGTACAAG	2083
1617	UGUACCGC A UAUGGUAU	382	ATACCATA GGCTAGCTACAACGA GCGGTACA	2084
1619	UACCGCAU A UGGUAUCC	383	GGATACCA GGCTAGCTACAACGA ATGCGGTA	2085
1622	CGCAUAUG G UAUCCCUC	384	GAGGGATA GGCTAGCTACAACGA CATATGCG	2086
1624	CAUAUGGU A UCCCUCAA	385	TTGAGGGA GGCTAGCTACAACGA ACCATATG	2087
1632	AUCCCUCA A CCUACAAU	386	ATTGTAGG GGCTAGCTACAACGA TGAGGGAT	2088
1636	CUCAACCU A CAAUCAAG	387	CTTGATTG GGCTAGCTACAACGA AGGTTGAG	2089
1639	AACCUACA A UCAAGUGG	388	CCACTTGA GGCTAGCTACAACGA TGTAGGTT	2090
1644	ACAAUCAA G UGGUUCUG	389	CAGAACCA GGCTAGCTACAACGA TTGATTGT	2091
1647	AUCAAGUG G UUCUGGCA	390	TGCCAGAA GGCTAGCTACAACGA CACTTGAT	2092
1653	UGGUUCUG G CACCCCUG	391	CAGGGGTG GGCTAGCTACAACGA CAGAACCA	2093
1655	GUUCUGGC A CCCCUGUA	392	TACAGGGG GGCTAGCTACAACGA GCCAGAAC	2094
1661	GCACCCCU G UAACCAUA	393	TATGGTTA GGCTAGCTACAACGA AGGGGTGC	2095
1664	CCCCUGUA A CCAUAAUC	394	GATTATGG GGCTAGCTACAACGA TACAGGGG	2096
1667	CUGUAACC A UAAUCAUU	395	AATGATTA GGCTAGCTACAACGA GGTTACAG	2097
1670	UAACCAUA A UCAUUCCG	396	CGGAATGA GGCTAGCTACAACGA TATGGTTA	2098
1673	CCAUAAUC A UUCCGAAG	397	CTTCGGAA GGCTAGCTACAACGA GATTATGG	2099
1681	AUUCCGAA G CAAGGUGU	398	ACACCTTG GGCTAGCTACAACGA TTCGGAAT	2100
1686	GAAGCAAG G UGUGACUU	399	AAGTCACA GGCTAGCTACAACGA CTTGCTTC	2101
1688	AGCAAGGU G UGACUUUU	400	AAAAGTCA GGCTAGCTACAACGA ACCTTGCT	2102
1691	AAGGUGUG A CUUUUGUU	401	AACAAAAG GGCTAGCTACAACGA CACACCTT	2103
1697	UGACUUUU G UUCCAAUA	402	TATTGGAA GGCTAGCTACAACGA AAAAGTCA	2104
1703	UUGUUCCA A UAAUGAAG	403	CTTCATTA GGCTAGCTACAACGA TGGAACAA	2105
1706	UUCCAAUA A UGAAGAGU	404	ACTCTTCA GGCTAGCTACAACGA TATTGGAA	2106
1713	AAUGAAGA G UCCUUUAU	405	ATAAAGGA GGCTAGCTACAACGA TCTTCATT	2107
1720	AGUCCUUU A UCCUGGAU	406	ATCCAGGA GGCTAGCTACAACGA AAAGGACT	2108
1727	UAUCCUGG A UGCUGACA	407	TGTCAGCA GGCTAGCTACAACGA CCAGGATA	2109
1729	UCCUGGAU G CUGACAGC	408	GCTGTCAG GGCTAGCTACAACGA ATCCAGGA	2110
1733	GGAUGCUG A CAGCAACA	409	TGTTGCTG GGCTAGCTACAACGA CAGCATCC	2111
1736	UGCUGACA G CAACAUGG	410	CCATGTTG GGCTAGCTACAACGA TGTCAGCA	2112
1739	UGACAGCA A CAUGGGAA	411	TTCCCATG GGCTAGCTACAACGA TGCTGTCA	2113
1741	ACAGCAAC A UGGGAAAC	412	GTTTCCCA GGCTAGCTACAACGA GTTGCTGT	2114

1748	CAUGGGAA A CAGAAUUG	413	CAATTCTG GGCTAGCTACAACGA TTCCCATG	2115
1753	GAAACAGA A UUGAGAGC	414	GCTCTCAA GGCTAGCTACAACGA TCTGTTTC	2116
1760	AAUUGAGA G CAUCACUC	415	GAGTGATG GGCTAGCTACAACGA TCTCAATT	2117
1762	UUGAGAGC A UCACUCAG	416	CTGAGTGA GGCTAGCTACAACGA GCTCTCAA	2118
1765	AGAGCAUC A CUCAGCGC	417	GCGCTGAG GGCTAGCTACAACGA GATGCTCT	2119
1770	AUCACUCA G CGCAUGGC	418	GCCATGCG GGCTAGCTACAACGA TGAGTGAT	2120
1772	CACUCAGC G CAUGGCAA	419	TTGCCATG GGCTAGCTACAACGA GCTGAGTG	2121
1774	CUCAGCGC A UGGCAAUA	420	TATTGCCA GGCTAGCTACAACGA GCGCTGAG	2122
1777	AGCGCAUG G CAAUAAUA	421	TATTATTG GGCTAGCTACAACGA CATGCGCT	2123
1780	GCAUGGCA A UAAUAGAA	422	TTCTATTA GGCTAGCTACAACGA TGCCATGC	2124
1783	UGGCAAUA A UAGAAGGA	423	TCCTTCTA GGCTAGCTACAACGA TATTGCCA	2125
1796	AGGAAAGA A UAAGAUGG	424	CCATCTTA GGCTAGCTACAACGA TCTTTCCT	2126
1801	AGAAUAAG A UGGCUAGC	425	GCTAGCCA GGCTAGCTACAACGA CTTATTCT	2127
1804	AUAAGAUG G CUAGCACC	426	GGTGCTAG GGCTAGCTACAACGA CATCTTAT	2128
1808	GAUGGCUA G CACCUUGG	427	CCAAGGTG GGCTAGCTACAACGA TAGCCATC	2129
1810	UGGCUAGC A CCUUGGUU	428	AACCAAGG GGCTAGCTACAACGA GCTAGCCA	2130
1816	GCACCUUG G UUGUGGCU	429	AGCCACAA GGCTAGCTACAACGA CAAGGTGC	2131
1819	CCUUGGUU G UGGCUGAC	430	GTCAGCCA GGCTAGCTACAACGA AACCAAGG	2132
1822	UGGUUGUG G CUGACUCU	431	AGAGTCAG GGCTAGCTACAACGA CACAACCA	2133
1826	UGUGGCUG A CUCUAGAA	432	TTCTAGAG GGCTAGCTACAACGA CAGCCACA	2134
1834	ACUCUAGA A UUUCUGGA	433	TCCAGAAA GGCTAGCTACAACGA TCTAGAGT	2135
1843	UUUCUGGA A UCUACAUU	434	AATGTAGA GGCTAGCTACAACGA TCCAGAAA	2136
1847	UGGAAUCU A CAUUUGCA	435	TGCAAATG GGCTAGCTACAACGA AGATTCCA	2137
1849	GAAUCUAC A UUUGCAUA	436	TATGCAAA GGCTAGCTACAACGA GTAGATTC	2138
1853	CUACAUUU G CAUAGCUU	437	AAGCTATG GGCTAGCTACAACGA AAATGTAG	2139
1855	ACAUUUGC A UAGCUUCC	438	GGAAGCTA GGCTAGCTACAACGA GCAAATGT	2140
1858	UUUGCAUA G CUUCCAAU	439	ATTGGAAG GGCTAGCTACAACGA TATGCAAA	2141
1865	AGCUUCCA A UAAAGUUG	440	CAACTTTA GGCTAGCTACAACGA TGGAAGCT	2142
1870	CCAAUAAA G UUGGGACU	441	AGTCCCAA GGCTAGCTACAACGA TTTATTGG	2143
1876	AAGUUGGG A CUGUGGGA	442	TCCCACAG GGCTAGCTACAACGA CCCAACTT	2144
1879	UUGGGACU G UGGGAAGA	443	TCTTCCCA GGCTAGCTACAACGA AGTCCCAA	2145
1889	GGGAAGAA A CAUAAGCU	444	AGCTTATG GGCTAGCTACAACGA TTCTTCCC	2146
1891	GAAGAAAC A UAAGCUUU	445	AAAGCTTA GGCTAGCTACAACGA GTTTCTTC	2147
1895	AAACAUAA G CUUUUAUA	446	TATAAAAG GGCTAGCTACAACGA TTATGTTT	2148
1901	AAGCUUUU A UAUCACAG	447	CTGTGATA GGCTAGCTACAACGA AAAAGCTT	2149
1903	GCUUUUAU A UCACAGAU	448	ATCTGTGA GGCTAGCTACAACGA ATAAAAGC	2150
1906	UUUAUAUC A CAGAUGUG	449	CACATCTG GGCTAGCTACAACGA GATATAAA	2151
1910	UAUCACAG A UGUGCCAA	450	TTGGCACA GGCTAGCTACAACGA CTGTGATA	2152
1912	UCACAGAU G UGCCAAAU	451	ATTTGGCA GGCTAGCTACAACGA ATCTGTGA	2153
1914	ACAGAUGU G CCAAAUGG	452	CCATTTGG GGCTAGCTACAACGA ACATCTGT	2154
1919	UGUGCCAA A UGGGUUUC	453	GAAACCCA GGCTAGCTACAACGA TTGGCACA	2155
1923	CCAAAUGG G UUUCAUGU	454	ACATGAAA GGCTAGCTACAACGA CCATTTGG	2156
1928	UGGGUUUC A UGUUAACU	455	AGTTAACA GGCTAGCTACAACGA GAAACCCA	2157
1930	GGUUUCAU G UUAACUUG	456	CAAGTTAA GGCTAGCTACAACGA ATGAAACC	2158
1934	UCAUGUUA A CUUGGAAA	457	TTTCCAAG GGCTAGCTACAACGA TAACATGA	2159
1945	UGGAAAAA A UGCCGACG	458	CGTCGGCA GGCTAGCTACAACGA TTTTTCCA	2160
1947	GAAAAAAU G CCGACGGA	459	TCCGTCGG GGCTAGCTACAACGA ATTTTTTC	2161
1951	AAAUGCCG A CGGAAGGA	460	TCCTTCCG GGCTAGCTACAACGA CGGCATTT	2162
1964	AGGAGAGG A CCUGAAAC	461	GTTTCAGG GGCTAGCTACAACGA CCTCTCCT	2163
1971	GACCUGAA A CUGUCUUG	462	CAAGACAG GGCTAGCTACAACGA TTCAGGTC	2164
1974	CUGAAACU G UCUUGCAC	463	GTGCAAGA GGCTAGCTACAACGA AGTTTCAG	2165
1979	ACUGUCUU G CACAGUUA	464	TAACTGTG GGCTAGCTACAACGA AAGACAGT	2166

1981	UGUCUUGC A CAGUUAAC	465	GTTAACTG GGCTAGCTACAACGA GCAAGACA	2167
1984	CUUGCACA G UUAACAAG	466	CTTGTTAA GGCTAGCTACAACGA TGTGCAAG	2168
1988	CACAGUUA A CAAGUUCU	467	AGAACTTG GGCTAGCTACAACGA TAACTGTG	2169
1992	GUUAACAA G UUCUUAUA	468	TATAAGAA GGCTAGCTACAACGA TTGTTAAC	2170
1998	AAGUUCUU A UACAGAGA	469	TCTCTGTA GGCTAGCTACAACGA AAGAACTT	2171
2000	GUUCUUAU A CAGAGACG	470	CGTCTCTG GGCTAGCTACAACGA ATAAGAAC	2172
2006	AUACAGAG A CGUUACUU	471	AAGTAACG GGCTAGCTACAACGA CTCTGTAT	2173
2008	ACAGAGAC G UUACUUGG	472	CCAAGTAA GGCTAGCTACAACGA GTCTCTGT	2174
2011	GAGACGUU A CUUGGAUU	473	AATCCAAG GGCTAGCTACAACGA AACGTCTC	2175
2017	UUACUUGG A UUUUACUG	474	CAGTAAAA GGCTAGCTACAACGA CCAAGTAA	2176
2022	UGGAUUUU A CUGCGGAC	475	GTCCGCAG GGCTAGCTACAACGA AAAATCCA	2177
2025	AUUUUACU G CGGACAGU	476	ACTGTCCG GGCTAGCTACAACGA AGTAAAAT	2178
2029	UACUGCGG A CAGUUAAU	477	ATTAACTG GGCTAGCTACAACGA CCGCAGTA	2179
2032	UGCGGACA G UUAAUAAC	478	GTTATTAA GGCTAGCTACAACGA TGTCCGCA	2180
2036	GACAGUUA A UAACAGAA	479	TTCTGTTA GGCTAGCTACAACGA TAACTGTC	2181
2039	AGUUAAUA A CAGAACAA	480	TTGTTCTG GGCTAGCTACAACGA TATTAACT	2182
2044	AUAACAGA A CAAUGCAC	481	GTGCATTG GGCTAGCTACAACGA TCTGTTAT	2183
2047	ACAGAACA A UGCACUAC	482	GTAGTGCA GGCTAGCTACAACGA TGTTCTGT	2184
2049	AGAACAAU G CACUACAG	483	CTGTAGTG GGCTAGCTACAACGA ATTGTTCT	2185
2051	AACAAUGC A CUACAGUA	484	TACTGTAG GGCTAGCTACAACGA GCATTGTT	2186
2054	AAUGCACU A CAGUAUUA	485	TAATACTG GGCTAGCTACAACGA AGTGCATT	2187
2057	GCACUACA G UAUUAGCA	486	TGCTAATA GGCTAGCTACAACGA TGTAGTGC	2188
2059	ACUACAGU A UUAGCAAG	487	CTTGCTAA GGCTAGCTACAACGA ACTGTAGT	2189
2063	CAGUAUUA G CAAGCAAA	488	TTTGCTTG GGCTAGCTACAACGA TAATACTG	2190
2067	AUUAGCAA G CAAAAAAU	489	ATTTTTTG GGCTAGCTACAACGA TTGCTAAT	2191
2074	AGCAAAAA A UGGCCAUC	490	GATGGCCA GGCTAGCTACAACGA TTTTTGCT	2192
2077	AAAAAAUG G CCAUCACU	491	AGTGATGG GGCTAGCTACAACGA CATTTTTT	2193
2080	AAAUGGCC A UCACUAAG	492	CTTAGTGA GGCTAGCTACAACGA GGCCATTT	2194
2083	UGGCCAUC A CUAAGGAG	493	CTCCTTAG GGCTAGCTACAACGA GATGGCCA	2195
2091	ACUAAGGA G CACUCCAU	494	ATGGAGTG GGCTAGCTACAACGA TCCTTAGT	2196
2093	UAAGGAGC A CUCCAUCA	495	TGATGGAG GGCTAGCTACAACGA GCTCCTTA	2197
2098	AGCACUCC A UCACUCUU	496	AAGAGTGA GGCTAGCTACAACGA GGAGTGCT	2198
2101	ACUCCAUC A CUCUUAAU	497	ATTAAGAG GGCTAGCTACAACGA GATGGAGT	2199
2108	CACUCUUA A UCUUACCA	498	TGGTAAGA GGCTAGCTACAACGA TAAGAGTG	2200
2113	UUAAUCUU A CCAUCAUG	499	CATGATGG GGCTAGCTACAACGA AAGATTAA	2201
2116	AUCUUACC A UCAUGAAU	500	ATTCATGA GGCTAGCTACAACGA GGTAAGAT	2202
2119	UUACCAUC A UGAAUGUU	501	AACATTCA GGCTAGCTACAACGA GATGGTAA	2203
2123	CAUCAUGA A UGUUUCCC	502	GGGAAACA GGCTAGCTACAACGA TCATGATG	2204
2125	UCAUGAAU G UUUCCCUG	503	CAGGGAAA GGCTAGCTACAACGA ATTCATGA	2205
2133	GUUUCCCU G CAAGAUUC	504	GAATCTTG GGCTAGCTACAACGA AGGGAAAC	2206
2138	CCUGCAAG A UUCAGGCA	505	TGCCTGAA GGCTAGCTACAACGA CTTGCAGG	2207
2144	AGAUUCAG G CACCUAUG	506	CATAGGTG GGCTAGCTACAACGA CTGAATCT	2208
2146	AUUCAGGC A CCUAUGCC	507	GGCATAGG GGCTAGCTACAACGA GCCTGAAT	2209
2150	AGGCACCU A UGCCUGCA	508	TGCAGGCA GGCTAGCTACAACGA AGGTGCCT	2210
2152	GCACCUAU G CCUGCAGA	509	TCTGCAGG GGCTAGCTACAACGA ATAGGTGC	2211
2156	CUAUGCCU G CAGAGCCA	510	TGGCTCTG GGCTAGCTACAACGA AGGCATAG	2212
2161	CCUGCAGA G CCAGGAAU	511	ATTCCTGG GGCTAGCTACAACGA TCTGCAGG	2213
2168	AGCCAGGA A UGUAUACA	512	TGTATACA GGCTAGCTACAACGA TCCTGGCT	2214
2170	CCAGGAAU G UAUACACA	513	TGTGTATA GGCTAGCTACAACGA ATTCCTGG	2215
2172	AGGAAUGU A UACACAGG	514	CCTGTGTA GGCTAGCTACAACGA ACATTCCT	2216
2174	GAAUGUAU A CACAGGGG	515	CCCCTGTG GGCTAGCTACAACGA ATACATTC	2217
2176	AUGUAUAC A CAGGGGAA	516	TTCCCCTG GGCTAGCTACAACGA GTATACAT	2218

2188	GGGAAGAA A UCCUCCAG	517	CTGGAGGA GGCTAGCTACAACGA TTCTTCCC	2219
2206	AGAAAGAA A UUACAAUC	518	GATTGTAA GGCTAGCTACAACGA TTCTTTCT	2220
2209	AAGAAAUU A CAAUCAGA	519	TCTGATTG GGCTAGCTACAACGA AATTTCTT	2221
2212	AAAUUACA A UCAGAGAU	520	ATCTCTGA GGCTAGCTACAACGA TGTAATTT	2222
2219	AAUCAGAG A UCAGGAAG	521	CTTCCTGA GGCTAGCTACAACGA CTCTGATT	2223
2227	AUCAGGAA G CACCAUAC	522	GTATGGTG GGCTAGCTACAACGA TTCCTGAT	2224
2229	CAGGAAGC A CCAUACCU	523	AGGTATGG GGCTAGCTACAACGA GCTTCCTG	2225
2232	GAAGCACC A UACCUCCU	524	AGGAGGTA GGCTAGCTACAACGA GGTGCTTC	2226
2234	AGCACCAU A CCUCCUGC	525	GCAGGAGG GGCTAGCTACAACGA ATGGTGCT	2227
2241	UACCUCCU G CGAAACCU	526	AGGTTTCG GGCTAGCTACAACGA AGGAGGTA	2228
2246	CCUGCGAA A CCUCAGUG	527	CACTGAGG GGCTAGCTACAACGA TTCGCAGG	2229
2252	AAACCUCA G UGAUCACA	528	TGTGATCA GGCTAGCTACAACGA TGAGGTTT	2230
2255	CCUCAGUG A UCACACAG	529	CTGTGTGA GGCTAGCTACAACGA CACTGAGG	2231
2258	CAGUGAUC A CACAGUGG	530	CCACTGTG GGCTAGCTACAACGA GATCACTG	2232
2260	GUGAUCAC A CAGUGGCC	531	GGCCACTG GGCTAGCTACAACGA GTGATCAC	2233
2263	AUCACACA G UGGCCAUC	532	GATGGCCA GGCTAGCTACAACGA TGTGTGAT	2234
2266	ACACAGUG G CCAUCAGC	533	GCTGATGG GGCTAGCTACAACGA CACTGTGT	2235
2269	CAGUGGCC A UCAGCAGU	534	ACTGCTGA GGCTAGCTACAACGA GGCCACTG	2236
2273	GGCCAUCA G CAGUUCCA	535	TGGAACTG GGCTAGCTACAACGA TGATGGCC	2237
2276	CAUCAGCA G UUCCACCA	536	TGGTGGAA GGCTAGCTACAACGA TGCTGATG	2238
2281	GCAGUUCC A CCACUUUA	537	TAAAGTGG GGCTAGCTACAACGA GGAACTGC	2239
2284	GUUCCACC A CUUUAGAC	538	GTCTAAAG GGCTAGCTACAACGA GGTGGAAC	2240
2291	CACUUUAG A CUGUCAUG	539	CATGACAG GGCTAGCTACAACGA CTAAAGTG	2241
2294	UUUAGACU G UCAUGCUA	540	TAGCATGA GGCTAGCTACAACGA AGTCTAAA	2242
2297	AGACUGUC A UGCUAAUG	541	CATTAGCA GGCTAGCTACAACGA GACAGTCT	2243
2299	ACUGUCAU G CUAAUGGU	542	ACCATTAG GGCTAGCTACAACGA ATGACAGT	2244
2303	UCAUGCUA A UGGUGUCC	543	GGACACCA GGCTAGCTACAACGA TAGCATGA	2245
2306	UGCUAAUG G UGUCCCCG	544	CGGGGACA GGCTAGCTACAACGA CATTAGCA	2246
2308	CUAAUGGU G UCCCCGAG	545	CTCGGGGA GGCTAGCTACAACGA ACCATTAG	2247
2316	GUCCCCGA G CCUCAGAU	546	ATCTGAGG GGCTAGCTACAACGA TCGGGGAC	2248
2323	AGCCUCAG A UCACUUGG	547	CCAAGTGA GGCTAGCTACAACGA CTGAGGCT	2249
2326	CUCAGAUC A CUUGGUUU	548	AAACCAAG GGCTAGCTACAACGA GATCTGAG	2250
2331	AUCACUUG G UUUAAAAA	549	TTTTTAAA GGCTAGCTACAACGA CAAGTGAT	2251
2339	GUUUAAAA A CAACCACA	550	TGTGGTTG GGCTAGCTACAACGA TTTTAAAC	2252
2342	UAAAAACA A CCACAAAA	551	TTTTGTGG GGCTAGCTACAACGA TGTTTTTA	2253
2345	AAACAACC A CAAAAUAC	552	GTATTTTG GGCTAGCTACAACGA GGTTGTTT	2254
2350	ACCACAAA A UACAACAA	553	TTGTTGTA GGCTAGCTACAACGA TTTGTGGT	2255
2352	CACAAAAU A CAACAAGA	554	TCTTGTTG GGCTAGCTACAACGA ATTTTGTG	2256
2355	AAAAUACA A CAAGAGCC	555	GGCTCTTG GGCTAGCTACAACGA TGTATTTT	2257
2361	CAACAAGA G CCUGGAAU	556	ATTCCAGG GGCTAGCTACAACGA TCTTGTTG	2258
2368	AGCCUGGA A UUAUUUUA	557	TAAAATAA GGCTAGCTACAACGA TCCAGGCT	2259
2371	CUGGAAUU A UUUUAGGA	558	TCCTAAAA GGCTAGCTACAACGA AATTCCAG	2260
2379	AUUUUAGG A CCAGGAAG	559	CTTCCTGG GGCTAGCTACAACGA CCTAAAAT	2261
2387	ACCAGGAA G CAGCACGC	560	GCGTGCTG GGCTAGCTACAACGA TTCCTGGT	2262
2390	AGGAAGCA G CACGCUGU	561	ACAGCGTG GGCTAGCTACAACGA TGCTTCCT	2263
2392	GAAGCAGC A CGCUGUUU	562	AAACAGCG GGCTAGCTACAACGA GCTGCTTC	2264
2394	AGCAGCAC G CUGUUUAU	563	ATAAACAG GGCTAGCTACAACGA GTGCTGCT	2265
2397	AGCACGCU G UUUAUUGA	564	TCAATAAA GGCTAGCTACAACGA AGCGTGCT	2266
2401	CGCUGUUU A UUGAAAGA	565	TCTTTCAA GGCTAGCTACAACGA AAACAGCG	2267
2410	UUGAAAGA G UCACAGAA	566	TTCTGTGA GGCTAGCTACAACGA TCTTTCAA	2268
2413	AAAGAGUC A CAGAAGAG	567	CTCTTCTG GGCTAGCTACAACGA GACTCTTT	2269
2423	AGAAGAGG A UGAAGGUG	568	CACCTTCA GGCTAGCTACAACGA CCTCTTCT	2270

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2488	CAUACCUC A CUGUUCAA	583	TTGAACAG GGCTAGCTACAACGA GAGGTATG	2285
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2516	CAAGUCUA A UCUGGAGC	588	GCTCCAGA GGCTAGCTACAACGA TAGACTTG	2290
2523	AAUCUGGA G CUGAUCAC	589	GTGATCAG GGCTAGCTACAACGA TCCAGATT	2291
2527	UGGAGCUG A UCACUCUA	590	TAGAGTGA GGCTAGCTACAACGA CAGCTCCA	2292
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2538	ACUCUAAC A UGCACCUG	593	CAGGTGCA GGCTAGCTACAACGA GTTAGAGT	2295
2540	UCUAACAU G CACCUGUG	594	CACAGGTG GGCTAGCTACAACGA ATGTTAGA	2296
2542	UAACAUGC A CCUGUGUG	595	CACACAGG GGCTAGCTACAACGA GCATGTTA	2297
2546	AUGCACCU G UGUGGCUG	596	CAGCCACA GGCTAGCTACAACGA AGGTGCAT	2298
2548	GCACCUGU G UGGCUGCG	597	CGCAGCCA GGCTAGCTACAACGA ACAGGTGC	2299
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2554	GUGUGGCU G CGACUCUC	599	GAGAGTCG GGCTAGCTACAACGA AGCCACAC	2301
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2568	CUCUUCUG G CUCCUAUU	601	AATAGGAG GGCTAGCTACAACGA CAGAAGAG	2303
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2578	UCCUAUUA A CCCUCCUU	603	AAGGAGGG GGCTAGCTACAACGA TAATAGGA	2305
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2623	AAAUAAAG A CUGACUAC	608	GTAGTCAG GGCTAGCTACAACGA CTTTATTT	2310
2627	AAAGACUG A CUACCUAU	609	ATAGGTAG GGCTAGCTACAACGA CAGTCTTT	2311
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2634	GACUACCU A UCAAUUAU	611	ATAATTGA GGCTAGCTACAACGA AGGTAGTC	2313
2638	ACCUAUCA A UUAUAAUG	612	CATTATAA GGCTAGCTACAACGA TGATAGGT	2314
2641	UAUCAAUU A UAAUGGAC	613	GTCCATTA GGCTAGCTACAACGA AATTGATA	2315
2644	CAAUUAUA A UGGACCCA	614	TGGGTCCA GGCTAGCTACAACGA TATAATTG	2316
2648	UAUAAUGG A CCCAGAUG	615	CATCTGGG GGCTAGCTACAACGA CCATTATA	2317
2654	GGACCCAG A UGAAGUUC	616	GAACTTCA GGCTAGCTACAACGA CTGGGTCC	2318
2659	CAGAUGAA G UUCCUUUG	617	CAAAGGAA GGCTAGCTACAACGA TTCATCTG	2319
2669	UCCUUUGG A UGAGCAGU	618	ACTGCTCA GGCTAGCTACAACGA CCAAAGGA	2320
2673	UUGGAUGA G CAGUGUGA	619	TCACACTG GGCTAGCTACAACGA TCATCCAA	2321
2676	GAUGAGCA G UGUGAGCG	620	CGCTCACA GGCTAGCTACAACGA TGCTCATC	2322

2678	UGAGCAGU G UGAGCGGC	621	GCCGCTCA GGCTAGCTACAACGA ACTGCTCA	2323
2682	CAGUGUGA G CGGCUCCC	622	GGGAGCCG GGCTAGCTACAACGA TCACACTG	2324
2685	UGUGAGCG G CUCCCUUA	623	TAAGGGAG GGCTAGCTACAACGA CGCTCACA	2325
2693	GCUCCCUU A UGAUGCCA	624	TGGCATCA GGCTAGCTACAACGA AAGGGAGC	2326
2696	CCCUUAUG A UGCCAGCA	625	TGCTGGCA GGCTAGCTACAACGA CATAAGGG	2327
2698	CUUAUGAU G CCAGCAAG	626	CTTGCTGG GGCTAGCTACAACGA ATCATAAG	2328
2702	UGAUGCCA G CAAGUGGG	627	CCCACTTG GGCTAGCTACAACGA TGGCATCA	2329
2706	GCCAGCAA G UGGGAGUU	628	AACTCCCA GGCTAGCTACAACGA TTGCTGGC	2330
2712	AAGUGGGA G UUUGCCCG	629	CGGGCAAA GGCTAGCTACAACGA TCCCACTT	2331
2716	GGGAGUUU G CCCGGGAG	630	CTCCCGGG GGCTAGCTACAACGA AAACTCCC	2332
2727	CGGGAGAG A CUUAAACU	631	AGTTTAAG GGCTAGCTACAACGA CTCTCCCG	2333
2733	AGACUUAA A CUGGGCAA	632	TTGCCCAG GGCTAGCTACAACGA TTAAGTCT	2334
2738	UAAACUGG G CAAAUCAC	633	GTGATTTG GGCTAGCTACAACGA CCAGTTTA	2335
2742	CUGGGCAA A UCACUUGG	634	CCAAGTGA GGCTAGCTACAACGA TTGCCCAG	2336
2745	GGCAAAUC A CUUGGAAG	635	CTTCCAAG GGCTAGCTACAACGA GATTTGCC	2337
2758	GAAGAGGG G CUUUUGGA	636	TCCAAAAG GGCTAGCTACAACGA CCCTCTTC	2338
2770	UUGGAAAA G UGGUUCAA	637	TTGAACCA GGCTAGCTACAACGA TTTTCCAA	2339
2773	GAAAAGUG G UUCAAGCA	638	TGCTTGAA GGCTAGCTACAACGA CACTTTTC	2340
2779	UGGUUCAA G CAUCAGCA	639	TGCTGATG GGCTAGCTACAACGA TTGAACCA	2341
2781	GUUCAAGC A UCAGCAUU	640	AATGCTGA GGCTAGCTACAACGA GCTTGAAC	2342
2785	AAGCAUCA G CAUUUGGC	641	GCCAAATG GGCTAGCTACAACGA TGATGCTT	2343
2787	GCAUCAGC A UUUGGCAU	642	ATGCCAAA GGCTAGCTACAACGA GCTGATGC	2344
2792	AGCAUUUG G CAUUAAGA	643	TCTTAATG GGCTAGCTACAACGA CAAATGCT	2345
2794	CAUUUGGC A UUAAGAAA	644	TTTCTTAA GGCTAGCTACAACGA GCCAAATG	2346
2802	AUUAAGAA A UCACCUAC	645	GTAGGTGA GGCTAGCTACAACGA TTCTTAAT	2347
2805	AAGAAAUC A CCUACGUG	646	CACGTAGG GGCTAGCTACAACGA GATTTCTT	2348
2809	AAUCACCU A CGUGCCGG	647	CCGGCACG GGCTAGCTACAACGA AGGTGATT	2349
2811	UCACCUAC G UGCCGGAC	648	GTCCGGCA GGCTAGCTACAACGA GTAGGTGA	2350
2813	ACCUACGU G CCGGACUG	649	CAGTCCGG GGCTAGCTACAACGA ACGTAGGT	2351
2818	CGUGCCGG A CUGUGGCU	650	AGCCACAG GGCTAGCTACAACGA CCGGCACG	2352
2821	GCCGGACU G UGGCUGUG	651	CACAGCCA GGCTAGCTACAACGA AGTCCGGC	2353
2824	GGACUGUG G CUGUGAAA	652	TTTCACAG GGCTAGCTACAACGA CACAGTCC	2354
2827	CUGUGGCU G UGAAAAUG	653	CATTTTCA GGCTAGCTACAACGA AGCCACAG	2355
2833	CUGUGAAA A UGCUGAAA	654	TTTCAGCA GGCTAGCTACAACGA TTTCACAG	2356
2835	GUGAAAAU G CUGAAAGA	655	TCTTTCAG GGCTAGCTACAACGA ATTTTCAC	2357
2848	AAGAGGGG G CCACGGCC	656	GGCCGTGG GGCTAGCTACAACGA CCCCTCTT	2358
2851	AGGGGGCC A CGGCCAGC	657	GCTGGCCG GGCTAGCTACAACGA GGCCCCCT	2359
2854	GGGCCACG G CCAGCGAG	658	CTCGCTGG GGCTAGCTACAACGA CGTGGCCC	2360
2858	CACGGCCA G CGAGUACA	659	TGTACTCG GGCTAGCTACAACGA TGGCCGTG	2361
2862	GCCAGCGA G UACAAAGC	660	GCTTTGTA GGCTAGCTACAACGA TCGCTGGC	2362
2864	CAGCGAGU A CAAAGCUC	661	GAGCTTTG GGCTAGCTACAACGA ACTCGCTG	2363
2869	AGUACAAA G CUCUGAUG	662	CATCAGAG GGCTAGCTACAACGA TTTGTACT	2364
2875	AAGCUCUG A UGACUGAG	663	CTCAGTCA GGCTAGCTACAACGA CAGAGCTT	2365
2878	CUCUGAUG A CUGAGCUA	664	TAGCTCAG GGCTAGCTACAACGA CATCAGAG	2366
2883	AUGACUGA G CUAAAAAU	665	ATTTTTAG GGCTAGCTACAACGA TCAGTCAT	2367
2890	AGCUAAAA A UCUUGACC	666	GGTCAAGA GGCTAGCTACAACGA TTTTAGCT	2368
2896	AAAUCUUG A CCCACAUU	667	AATGTGGG GGCTAGCTACAACGA CAAGATTT	2369
2900	CUUGACCC A CAUUGGCC	668	GGCCAATG GGCTAGCTACAACGA GGGTCAAG	2370
2902	UGACCCAC A UUGGCCAC	669	GTGGCCAA GGCTAGCTACAACGA GTGGGTCA	2371
2906	CCACAUUG G CCACCAUC	670	GATGGTGG GGCTAGCTACAACGA CAATGTGG	2372
2909	CAUUGGCC A CCAUCUGA	671	TCAGATGG GGCTAGCTACAACGA GGCCAATG	2373
2912	UGGCCACC A UCUGAACG	672	CGTTCAGA GGCTAGCTACAACGA GGTGGCCA	2374

2918	CCAUCUGA A CGUGGUUA	673	TAACCACG GGCTAGCTACAACGA TCAGATGG	2375
2920	AUCUGAAC G UGGUUAAC	674	GTTAACCA GGCTAGCTACAACGA GTTCAGAT	2376
2923	UGAACGUG G UUAACCUG	675	CAGGTTAA GGCTAGCTACAACGA CACGTTCA	2377
2927	CGUGGUUA A CCUGCUGG	676	CCAGCAGG GGCTAGCTACAACGA TAACCACG	2378
2931	GUUAACCU G CUGGGAGC	677	GCTCCCAG GGCTAGCTACAACGA AGGTTAAC	2379
2938	UGCUGGGA G CCUGCACC	678	GGTGCAGG GGCTAGCTACAACGA TCCCAGCA	2380
2942	GGGAGCCU G CACCAAGC	679	GCTTGGTG GGCTAGCTACAACGA AGGCTCCC	2381
2944	GAGCCUGC A CCAAGCAA	680	TTGCTTGG GGCTAGCTACAACGA GCAGGCTC	2382
2949	UGCACCAA G CAAGGAGG	681	CCTCCTTG GGCTAGCTACAACGA TTGGTGCA	2383
2958	CAAGGAGG G CCUCUGAU	682	ATCAGAGG GGCTAGCTACAACGA CCTCCTTG	2384
2965	GGCCUCUG A UGGUGAUU	683	AATCACCA GGCTAGCTACAACGA CAGAGGCC	2385
2968	CUCUGAUG G UGAUUGUU	684	AACAATCA GGCTAGCTACAACGA CATCAGAG	2386
2971	UGAUGGUG A UUGUUGAA	685	TTCAACAA GGCTAGCTACAACGA CACCATCA	2387
2974	UGGUGAUU G UUGAAUAC	686	GTATTCAA GGCTAGCTACAACGA AATCACCA	2388
2979	AUUGUUGA A UACUGCAA	687	TTGCAGTA GGCTAGCTACAACGA TCAACAAT	2389
2981	UGUUGAAU A CUGCAAAU	688	ATTTGCAG GGCTAGCTACAACGA ATTCAACA	2390
2984	UGAAUACU G CAAAUAUG	689	CATATTTG GGCTAGCTACAACGA AGTATTCA	2391
2988	UACUGCAA A UAUGGAAA	690	TTTCCATA GGCTAGCTACAACGA TTGCAGTA	2392
2990	CUGCAAAU A UGGAAAUC	691	GATTTCCA GGCTAGCTACAACGA ATTTGCAG	2393
2996	AUAUGGAA A UCUCUCCA	692	TGGAGAGA GGCTAGCTACAACGA TTCCATAT	2394
3005	UCUCUCCA A CUACCUCA	693	TGAGGTAG GGCTAGCTACAACGA TGGAGAGA	2395
3008	CUCCAACU A CCUCAAGA	694	TCTTGAGG GGCTAGCTACAACGA AGTTGGAG	2396
3017	CCUCAAGA G CAAACGUG	695	CACGTTTG GGCTAGCTACAACGA TCTTGAGG	2397
3021	AAGAGCAA A CGUGACUU	696	AAGTCACG GGCTAGCTACAACGA TTGCTCTT	2398
3023	GAGCAAAC G UGACUUAU	697	ATAAGTCA GGCTAGCTACAACGA GTTTGCTC	2399
3026	CAAACGUG A CUUAUUUU	698	AAAATAAG GGCTAGCTACAACGA CACGTTTG	2400
3030	CGUGACUU A UUUUUUCU	699	AGAAAAAA GGCTAGCTACAACGA AAGTCACG	2401
3041	UUUUCUCA A CAAGGAUG	700	CATCCTTG GGCTAGCTACAACGA TGAGAAAA	2402
3047	CAACAAGG A UGCAGCAC	701	GTGCTGCA GGCTAGCTACAACGA CCTTGTTG	2403
3049	ACAAGGAU G CAGCACUA	702	TAGTGCTG GGCTAGCTACAACGA ATCCTTGT	2404
3052	AGGAUGCA G CACUACAC	703	GTGTAGTG GGCTAGCTACAACGA TGCATCCT	2405
3054	GAUGCAGC A CUACACAU	704	ATGTGTAG GGCTAGCTACAACGA GCTGCATC	2406
3057	GCAGCACU A CACAUGGA	705	TCCATGTG GGCTAGCTACAACGA AGTGCTGC	2407
3059	AGCACUAC A CAUGGAGC	706	GCTCCATG GGCTAGCTACAACGA GTAGTGCT	2408
3061	CACUACAC A UGGAGCCU	707	AGGCTCCA GGCTAGCTACAACGA GTGTAGTG	2409
3066	CACAUGGA G CCUAAGAA	708	TTCTTAGG GGCTAGCTACAACGA TCCATGTG	2410
3082	AAGAAAAA A UGGAGCCA	709	TGGCTCCA GGCTAGCTACAACGA TTTTTCTT	2411
3087	AAAAUGGA G CCAGGCCU	710	AGGCCTGG GGCTAGCTACAACGA TCCATTTT	2412
3092	GGAGCCAG G CCUGGAAC	711	GTTCCAGG GGCTAGCTACAACGA CTGGCTCC	2413
3099	GGCCUGGA A CAAGGCAA	712	TTGCCTTG GGCTAGCTACAACGA TCCAGGCC	2414
3104	GGAACAAG G CAAGAAAC	713	GTTTCTTG GGCTAGCTACAACGA CTTGTTCC	2415
3111	GGCAAGAA A CCAAGACU	714	AGTCTTGG GGCTAGCTACAACGA TTCTTGCC	2416
3117	AAACCAAG A CUAGAUAG	715	CTATCTAG GGCTAGCTACAACGA CTTGGTTT	2417
3122	AAGACUAG A UAGCGUCA	716	TGACGCTA GGCTAGCTACAACGA CTAGTCTT	2418
3125	ACUAGAUA G CGUCACCA	717	TGGTGACG GGCTAGCTACAACGA TATCTAGT	2419
3127	UAGAUAGC G UCACCAGC	718	GCTGGTGA GGCTAGCTACAACGA GCTATCTA	2420
3130	AUAGCGUC A CCAGCAGC	719	GCTGCTGG GGCTAGCTACAACGA GACGCTAT	2421
3134	CGUCACCA G CAGCGAAA	720	TTTCGCTG GGCTAGCTACAACGA TGGTGACG	2422
3137	CACCAGCA G CGAAAGCU	721	AGCTTTCG GGCTAGCTACAACGA TGCTGGTG	2423
3143	CAGCGAAA G CUUUGCGA	722	TCGCAAAG GGCTAGCTACAACGA TTTCGCTG	2424
3148	AAAGCUUU G CGAGCUCC	723	GGAGCTCG GGCTAGCTACAACGA AAAGCTTT	2425
3152	CUUUGCGA G CUCCGGCU	724	AGCCGGAG GGCTAGCTACAACGA TCGCAAAG	2426

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3176	AGAUAAAA G UCUGAGUG	727	CACTCAGA GGCTAGCTACAACGA TTTTATCT	2429
3182	AAGUCUGA G UGAUGUUG	728	CAACATCA GGCTAGCTACAACGA TCAGACTT	2430
3185	UCUGAGUG A UGUUGAGG	729	CCTCAACA GGCTAGCTACAACGA CACTCAGA	2431
3187	UGAGUGAU G UUGAGGAA	730	TTCCTCAA GGCTAGCTACAACGA ATCACTCA	2432
3203	AGAGGAGG A UUCUGACG	731	CGTCAGAA GGCTAGCTACAACGA CCTCCTCT	2433
3209	GGAUUCUG A CGGUUUCU	732	AGAAACCG GGCTAGCTACAACGA CAGAATCC	2434
3212	UUCUGACG G UUUCUACA	733	TGTAGAAA GGCTAGCTACAACGA CGTCAGAA	2435
3218	CGGUUUCU A CAAGGAGC	734	GCTCCTTG GGCTAGCTACAACGA AGAAACCG	2436
3225	UACAAGGA G CCCAUCAC	735	GTGATGGG GGCTAGCTACAACGA TCCTTGTA	2437
3229	AGGAGCCC A UCACUAUG	736	CATAGTGA GGCTAGCTACAACGA GGGCTCCT	2438
3232	AGCCCAUC A CUAUGGAA	737	TTCCATAG GGCTAGCTACAACGA GATGGGCT	2439
3235	CCAUCACU A UGGAAGAU	738	ATCTTCCA GGCTAGCTACAACGA AGTGATGG	2440
3242	UAUGGAAG A UCUGAUUU	739	AAATCAGA GGCTAGCTACAACGA CTTCCATA	2441
3247	AAGAUCUG A UUUCUUAC	740	GTAAGAAA GGCTAGCTACAACGA CAGATCTT	2442
3254	GAUUUCUU A CAGUUUUC	741	GAAAACTG GGCTAGCTACAACGA AAGAAATC	2443
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3265	GUUUUCAA G UGGCCAGA	743	TCTGGCCA GGCTAGCTACAACGA TTGAAAAC	2445
3268	UUCAAGUG G CCAGAGGC	744	GCCTCTGG GGCTAGCTACAACGA CACTTGAA	2446
3275	GGCCAGAG G CAUGGAGU	745	ACTCCATG GGCTAGCTACAACGA CTCTGGCC	2447
3277	CCAGAGGC A UGGAGUUC	746	GAACTCCA GGCTAGCTACAACGA GCCTCTGG	2448
3282	GGCAUGGA G UUCCUGUC	747	GACAGGAA GGCTAGCTACAACGA TCCATGCC	2449
3288	GAGUUCCU G UCUUCCAG	748	CTGGAAGA GGCTAGCTACAACGA AGGAACTC	2450
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3304	GAAAGUGC A UUCAUCGG	751	CCGATGAA GGCTAGCTACAACGA GCACTTTC	2453
3308	GUGCAUUC A UCGGGACC	752	GGTCCCGA GGCTAGCTACAACGA GAATGCAC	2454
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3319	GGGACCUG G CAGCGAGA	754	TCTCGCTG GGCTAGCTACAACGA CAGGTCCC	2456
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3352	AGAACAAC G UGGUGAAG	761	CTTCACCA GGCTAGCTACAACGA GTTGTTCT	2463
3355	ACAACGUG G UGAAGAUU	762	AATCTTCA GGCTAGCTACAACGA CACGTTGT	2464
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3407	CCCCGAUU A UGUGAGAA	773	TTCTCACA GGCTAGCTACAACGA AATCGGGG	2475
3409	CCGAUUAU G UGAGAAAA	774	TTTTCTCA GGCTAGCTACAACGA ATAATCGG	2476
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3467	UAUCUUUG A CAAAAUCU	783	AGATTTTG GGCTAGCTACAACGA CAAAGATA	2485
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3495	AGCGACGU G UGGUCUUA	791	TAAGACCA GGCTAGCTACAACGA ACGTCGCT	2493
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3503	GUGGUCUU A CGGAGUAU	793	ATACTCCG GGCTAGCTACAACGA AAGACCAC	2495
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3634	CUCCUGAA A UCUAUCAG	818	CTGATAGA GGCTAGCTACAACGA TTCAGGAG	2520
3638	UGAAAUCU A UCAGAUCA	819	TGATCTGA GGCTAGCTACAACGA AGATTTCA	2521
3643	UCUAUCAG A UCAUGCUG	820	CAGCATGA GGCTAGCTACAACGA CTGATAGA	2522
3646	AUCAGAUC A UGCUGGAC	821	GTCCAGCA GGCTAGCTACAACGA GATCTGAT	2523
3648	CAGAUCAU G CUGGACUG	822	CAGTCCAG GGCTAGCTACAACGA ATGATCTG	2524
3653	CAUGCUGG A CUGCUGGC	823	GCCAGCAG GGCTAGCTACAACGA CCAGCATG	2525
3656	GCUGGACU G CUGGCACA	824	TGTGCCAG GGCTAGCTACAACGA AGTCCAGC	2526
3660	GACUGCUG G CACAGAGA	825	TCTCTGTG GGCTAGCTACAACGA CAGCAGTC	2527
3662	CUGCUGGC A CAGAGACC	826	GGTCTCTG GGCTAGCTACAACGA GCCAGCAG	2528
3668	GCACAGAG A CCCAAAAG	827	CTTTTGGG GGCTAGCTACAACGA CTCTGTGC	2529
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3700	CAGAACUU G UGGAAAAA	832	TTTTTCCA GGCTAGCTACAACGA AAGTTCTG	2534
3708	GUGGAAAA A CUAGGUGA	833	TCACCTAG GGCTAGCTACAACGA TTTTCCAC	2535
3713	AAAACUAG G UGAUUUGC	834	GCAAATCA GGCTAGCTACAACGA CTAGTTTT	2536
3716	ACUAGGUG A UUUGCUUC	835	GAAGCAAA GGCTAGCTACAACGA CACCTAGT	2537
3720	GGUGAUUU G CUUCAAGC	836	GCTTGAAG GGCTAGCTACAACGA AAATCACC	2538
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3735	GCAAAUGU A CAACAGGA	840	TCCTGTTG GGCTAGCTACAACGA ACATTTGC	2542
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3743	ACAACAGG A UGGUAAAG	842	CTTTACCA GGCTAGCTACAACGA CCTGTTGT	2544
3746	ACAGGAUG G UAAAGACU	843	AGTCTTTA GGCTAGCTACAACGA CATCCTGT	2545
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3755	UAAAGACU A CAUCCCAA	845	TTGGGATG GGCTAGCTACAACGA AGTCTTTA	2547
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3769	CAAUCAAU G CCAUACUG	849	CAGTATGG GGCTAGCTACAACGA ATTGATTG	2551
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3778	CCAUACUG A CAGGAAAU	852	ATTTCCTG GGCTAGCTACAACGA CAGTATGG	2554
3785	GACAGGAA A UAGUGGGU	853	ACCCACTA GGCTAGCTACAACGA TTCCTGTC	2555
3788	AGGAAAUA G UGGGUUUA	854	TAAACCCA GGCTAGCTACAACGA TATTTCCT	2556
3792	AAUAGUGG G UUUACAUA	855	TATGTAAA GGCTAGCTACAACGA CCACTATT	2557
3796	GUGGGUUU A CAUACUCA	856	TGAGTATG GGCTAGCTACAACGA AAACCCAC	2558
3798	GGGUUUAC A UACUCAAC	857	GTTGAGTA GGCTAGCTACAACGA GTAAACCC	2559
3800	GUUUACAU A CUCAACUC	858	GAGTTGAG GGCTAGCTACAACGA ATGTAAAC	2560
3805	CAUACUCA A CUCCUGCC	859	GGCAGGAG GGCTAGCTACAACGA TGAGTATG	2561
3811	CAACUCCU G CCUUCUCU	860	AGAGAAGG GGCTAGCTACAACGA AGGAGTTG	2562
3824	CUCUGAGG A CUUCUUCA	861	TGAAGAAG GGCTAGCTACAACGA CCTCAGAG	2563
3839	CAAGGAAA G UAUUUCAG	862	CTGAAATA GGCTAGCTACAACGA TTTCCTTG	2564
3841	AGGAAAGU A UUUCAGCU	863	AGCTGAAA GGCTAGCTACAACGA ACTTTCCT	2565
3847	GUAUUUCA G CUCCGAAG	864	CTTCGGAG GGCTAGCTACAACGA TGAAATAC	2566
3855	GCUCCGAA G UUUAAUUC	865	GAATTAAA GGCTAGCTACAACGA TTCGGAGC	2567
3860	GAAGUUUA A UUCAGGAA	866	TTCCTGAA GGCTAGCTACAACGA TAAACTTC	2568
3869	UUCAGGAA G CUCUGAUG	867	CATCAGAG GGCTAGCTACAACGA TTCCTGAA	2569
3875	AAGCUCUG A UGAUGUCA	868	TGACATCA GGCTAGCTACAACGA CAGAGCTT	2570
3878	CUCUGAUG A UGUCAGAU	869	ATCTGACA GGCTAGCTACAACGA CATCAGAG	2571
3880	CUGAUGAU G UCAGAUAU	870	ATATCTGA GGCTAGCTACAACGA ATCATCAG	2572
3885	GAUGUCAG A UAUGUAAA	871	TTTACATA GGCTAGCTACAACGA CTGACATC	2573
3887	UGUCAGAU A UGUAAAUG	872	CATTTACA GGCTAGCTACAACGA ATCTGACA	2574
3889	UCAGAUAU G UAAAUGCU	873	AGCATTTA GGCTAGCTACAACGA ATATCTGA	2575
3893	AUAUGUAA A UGCUUUCA	874	TGAAAGCA GGCTAGCTACAACGA TTACATAT	2576
3895	AUGUAAAU G CUUUCAAG	875	CTTGAAAG GGCTAGCTACAACGA ATTTACAT	2577
3903	GCUUUCAA G UUCAUGAG	876	CTCATGAA GGCTAGCTACAACGA TTGAAAGC	2578
3907	UCAAGUUC A UGAGCCUG	877	CAGGCTCA GGCTAGCTACAACGA GAACTTGA	2579
3911	GUUCAUGA G CCUGGAAA	878	TTTCCAGG GGCTAGCTACAACGA TCATGAAC	2580
3922	UGGAAAGA A UCAAAACC	879	GGTTTTGA GGCTAGCTACAACGA TCTTTCCA	2581
3928	GAAUCAAA A CCUUUGAA	880	TTCAAAGG GGCTAGCTACAACGA TTTGATTC	2582

3939	UUUGAAGA A CUUUUACC	881	GGTAAAAG GGCTAGCTACAACGA TCTTCAAA	2583
3945	GAACUUUU A CCGAAUGC	882	GCATTCGG GGCTAGCTACAACGA AAAAGTTC	2584
3950	UUUACCGA A UGCCACCU	883	AGGTGGCA GGCTAGCTACAACGA TCGGTAAA	2585
3952	UACCGAAU G CCACCUCC	884	GGAGGTGG GGCTAGCTACAACGA ATTCGGTA	2586
3955	CGAAUGCC A CCUCCAUG	885	CATGGAGG GGCTAGCTACAACGA GGCATTCG	2587
3961	CCACCUCC A UGUUUGAU	886	ATCAAACA GGCTAGCTACAACGA GGAGGTGG	2588
3963	ACCUCCAU G UUUGAUGA	887	TCATCAAA GGCTAGCTACAACGA ATGGAGGT	2589
3968	CAUGUUUG A UGACUACC	888	GGTAGTCA GGCTAGCTACAACGA CAAACATG	2590
3971	GUUUGAUG A CUACCAGG	889	CCTGGTAG GGCTAGCTACAACGA CATCAAAC	2591
3974	UGAUGACU A CCAGGGCG	890	CGCCCTGG GGCTAGCTACAACGA AGTCATCA	2592
3980	CUACCAGG G CGACAGCA	891	TGCTGTCG GGCTAGCTACAACGA CCTGGTAG	2593
3983	CCAGGGCG A CAGCAGCA	892	TGCTGCTG GGCTAGCTACAACGA CGCCCTGG	2594
3986	GGGCGACA G CAGCACUC	893	GAGTGCTG GGCTAGCTACAACGA TGTCGCCC	2595
3989	CGACAGCA G CACUCUGU	894	ACAGAGTG GGCTAGCTACAACGA TGCTGTCG	2596
3991	ACAGCAGC A CUCUGUUG	895	CAACAGAG GGCTAGCTACAACGA GCTGCTGT	2597
3996	AGCACUCU G UUGGCCUC	896	GAGGCCAA GGCTAGCTACAACGA AGAGTGCT	2598
4000	CUCUGUUG G CCUCUCCC	897	GGGAGAGG GGCTAGCTACAACGA CAACAGAG	2599
4009	CCUCUCCC A UGCUGAAG	898	CTTCAGCA GGCTAGCTACAACGA GGGAGAGG	2600
4011	UCUCCCAU G CUGAAGCG	899	CGCTTCAG GGCTAGCTACAACGA ATGGGAGA	2601
4017	AUGCUGAA G CGCUUCAC	900	GTGAAGCG GGCTAGCTACAACGA TTCAGCAT	2602
4019	GCUGAAGC G CUUCACCU	901	AGGTGAAG GGCTAGCTACAACGA GCTTCAGC	2603
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4030	UCACCUGG A CUGACAGC	903	GCTGTCAG GGCTAGCTACAACGA CCAGGTGA	2605
4034	CUGGACUG A CAGCAAAC	904	GTTTGCTG GGCTAGCTACAACGA CAGTCCAG	2606
4037	GACUGACA G CAAACCCA	905	TGGGTTTG GGCTAGCTACAACGA TGTCAGTC	2607
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4048	AACCCAAG G CCUCGCUC	907	GAGCGAGG GGCTAGCTACAACGA CTTGGGTT	2609
4053	AAGGCCUC G CUCAAGAU	908	ATCTTGAG GGCTAGCTACAACGA GAGGCCTT	2610
4060	CGCUCAAG A UUGACUUG	909	CAAGTCAA GGCTAGCTACAACGA CTTGAGCG	2611
4064	CAAGAUUG A CUUGAGAG	910	CTCTCAAG GGCTAGCTACAACGA CAATCTTG	2612
4072	ACUUGAGA G UAACCAGU	911	ACTGGTTA GGCTAGCTACAACGA TCTCAAGT	2613
4075	UGAGAGUA A CCAGUAAA	912	TTTACTGG GGCTAGCTACAACGA TACTCTCA	2614
4079	AGUAACCA G UAAAAGUA	913	TACTTTTA GGCTAGCTACAACGA TGGTTACT	2615
4085	CAGUAAAA G UAAGGAGU	914	ACTCCTTA GGCTAGCTACAACGA TTTTACTG	2616
4092	AGUAAGGA G UCGGGGCU	915	AGCCCCGA GGCTAGCTACAACGA TCCTTACT	2617
4098	GAGUCGGG G CUGUCUGA	916	TCAGACAG GGCTAGCTACAACGA CCCGACTC	2618
4101	UCGGGGCU G UCUGAUGU	917	ACATCAGA GGCTAGCTACAACGA AGCCCCGA	2619
4106	GCUGUCUG A UGUCAGCA	918	TGCTGACA GGCTAGCTACAACGA CAGACAGC	2620
4108	UGUCUGAU G UCAGCAGG	919	CCTGCTGA GGCTAGCTACAACGA ATCAGACA	2621
4112	UGAUGUCA G CAGGCCCA	920	TGGGCCTG GGCTAGCTACAACGA TGACATCA	2622
4116	GUCAGCAG G CCCAGUUU	921	AAACTGGG GGCTAGCTACAACGA CTGCTGAC	2623
4121	CAGGCCCA G UUUCUGCC	922	GGCAGAAA GGCTAGCTACAACGA TGGGCCTG	2624
4127	CAGUUUCU G CCAUUCCA	923	TGGAATGG GGCTAGCTACAACGA AGAAACTG	2625
4130	UUUCUGCC A UUCCAGCU	924	AGCTGGAA GGCTAGCTACAACGA GGCAGAAA	2626
4136	CCAUUCCA G CUGUGGGC	925	GCCCACAG GGCTAGCTACAACGA TGGAATGG	2627
4139	UUCCAGCU G UGGGCACG	926	CGTGCCCA GGCTAGCTACAACGA AGCTGGAA	2628
4143	AGCUGUGG G CACGUCAG	927	CTGACGTG GGCTAGCTACAACGA CCACAGCT	2629
4145	CUGUGGGC A CGUCAGCG	928	CGCTGACG GGCTAGCTACAACGA GCCCACAG	2630
4147	GUGGGCAC G UCAGCGAA	929	TTCGCTGA GGCTAGCTACAACGA GTGCCCAC	2631
4151	GCACGUCA G CGAAGGCA	930	TGCCTTCG GGCTAGCTACAACGA TGACGTGC	2632
4157	CAGCGAAG G CAAGCGCA	931	TGCGCTTG GGCTAGCTACAACGA CTTCGCTG	2633
4161	GAAGGCAA G CGCAGGUU	932	AACCTGCG GGCTAGCTACAACGA TTGCCTTC	2634

4163	AGGCAAGC G CAGGUUCA	933	TGAACCTG GGCTAGCTACAACGA GCTTGCCT	2635
4167	AAGCGCAG G UUCACCUA	934	TAGGTGAA GGCTAGCTACAACGA CTGCGCTT	2636
4171	GCAGGUUC A CCUACGAC	935	GTCGTAGG GGCTAGCTACAACGA GAACCTGC	2637
4175	GUUCACCU A CGACCACG	936	CGTGGTCG GGCTAGCTACAACGA AGGTGAAC	2638
4178	CACCUACG A CCACGCUG	937	CAGCGTGG GGCTAGCTACAACGA CGTAGGTG	2639
4181	CUACGACC A CGCUGAGC	938	GCTCAGCG GGCTAGCTACAACGA GGTCGTAG	2640
4183	ACGACCAC G CUGAGCUG	939	CAGCTCAG GGCTAGCTACAACGA GTGGTCGT	2641
4188	CACGCUGA G CUGGAAAG	940	CTTTCCAG GGCTAGCTACAACGA TCAGCGTG	2642
4201	AAAGGAAA A UCGCGUGC	941	GCACGCGA GGCTAGCTACAACGA TTTCCTTT	2643
4204	GGAAAAUC G CGUGCUGC	942	GCAGCACG GGCTAGCTACAACGA GATTTTCC	2644
4206	AAAAUCGC G UGCUGCUC	943	GAGCAGCA GGCTAGCTACAACGA GCGATTTT	2645
4208	AAUCGCGU G CUGCUCCC	944	GGGAGCAG GGCTAGCTACAACGA ACGCGATT	2646
4211	CGCGUGCU G CUCCCCGC	945	GCGGGGAG GGCTAGCTACAACGA AGCACGCG	2647
4218	UGCUCCCC G CCCCCAGA	946	TCTGGGGG GGCTAGCTACAACGA GGGGAGCA	2648
4226	GCCCCCAG A CUACAACU	947	AGTTGTAG GGCTAGCTACAACGA CTGGGGGC	2649
4229	CCCAGACU A CAACUCGG	948	CCGAGTTG GGCTAGCTACAACGA AGTCTGGG	2650
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4240	ACUCGGUG G UCCUGUAC	951	GTACAGGA GGCTAGCTACAACGA CACCGAGT	2653
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4247	GGUCCUGU A CUCCACCC	953	GGGTGGAG GGCTAGCTACAACGA ACAGGACC	2655
4252	UGUACUCC A CCCCACCC	954	GGGTGGGG GGCTAGCTACAACGA GGAGTACA	2656
4257	UCCACCCC A CCCAUCUA	955	TAGATGGG GGCTAGCTACAACGA GGGGTGGA	2657
4261	CCCCACCC A UCUAGAGU	956	ACTCTAGA GGCTAGCTACAACGA GGGTGGGG	2658
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4275	AGUUUGAC A CGAAGCCU	959	AGGCTTCG GGCTAGCTACAACGA GTCAAACT	2661
4280	GACACGAA G CCUUAUUU	960	AAATAAGG GGCTAGCTACAACGA TTCGTGTC	2662
4285	GAAGCCUU A UUUCUAGA	961	TCTAGAAA GGCTAGCTACAACGA AAGGCTTC	2663
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4297	CUAGAAGC A CAUGUGUA	963	TACACATG GGCTAGCTACAACGA GCTTCTAG	2665
4299	AGAAGCAC A UGUGUAUU	964	AATACACA GGCTAGCTACAACGA GTGCTTCT	2666
4301	AAGCACAU G UGUAUUUA	965	TAAATACA GGCTAGCTACAACGA ATGTGCTT	2667
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4311	GUAUUUAU A CCCCCAGG	969	CCTGGGGG GGCTAGCTACAACGA ATAAATAC	2671
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4326	GGAAACUA G CUUUUGCC	971	GGCAAAAG GGCTAGCTACAACGA TAGTTTCC	2673
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4336	UUUUGCCA G UAUUAUGC	973	GCATAATA GGCTAGCTACAACGA TGGCAAAA	2675
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4365	ACACCUUU A UCUUUCCA	983	TGGAAAGA GGCTAGCTACAACGA AAAGGTGT	2685
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4386	AGCCAGCU G CUUUUUGU	987	ACAAAAAG GGCTAGCTACAACGA AGCTGGCT	2689
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4396	UUUUUGUG A UUUUUUUA	989	TAAAAAAA GGCTAGCTACAACGA CACAAAAA	2691
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4550	CAACCCCC G CCACCUCA	1019	TGAGGTGG GGCTAGCTACAACGA GGGGGTTG	2721
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4579	CCAGUUUG A UUGAGGAG	1026	CTCCTCAA GGCTAGCTACAACGA CAAACTGG	2728
4587	AUUGAGGA G CUGCACUG	1027	CAGTGCAG GGCTAGCTACAACGA TCCTCAAT	2729
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4613	UGCAUCAC G UACCCCAC	1036	GTGGGGTA GGCTAGCTACAACGA GTGATGCA	2738

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4845	GCUCAGCA A UGCCAUUU	1078	AAATGGCA GGCTAGCTACAACGA TGCTGAGC	2780
4847	UCAGCAAU G CCAUUUCA	1079	TGAAATGG GGCTAGCTACAACGA ATTGCTGA	2781
4850	GCAAUGCC A UUUCAGUG	1080	CACTGAAA GGCTAGCTACAACGA GGCATTGC	2782
4856	CCAUUUCA G UGGCUUCC	1081	GGAAGCCA GGCTAGCTACAACGA TGAAATGG	2783
4859	UUUCAGUG G CUUCCCAG	1082	CTGGGAAG GGCTAGCTACAACGA CACTGAAA	2784
4867	GCUUCCCA G CUCUGACC	1083	GGTCAGAG GGCTAGCTACAACGA TGGGAAGC	2785
4873	CAGCUCUG A CCCUUCUA	1084	TAGAAGGG GGCTAGCTACAACGA CAGAGCTG	2786
4881	ACCCUUCU A CAUUUGAG	1085	CTCAAATG GGCTAGCTACAACGA AGAAGGGT	2787
4883	CCUUCUAC A UUUGAGGG	1086	CCCTCAAA GGCTAGCTACAACGA GTAGAAGG	2788
4891	AUUUGAGG G CCCAGCCA	1087	TGGCTGGG GGCTAGCTACAACGA CCTCAAAT	2789
4896	AGGGCCCA G CCAGGAGC	1088	GCTCCTGG GGCTAGCTACAACGA TGGGCCCT	2790

4903	AGCCAGGA G CAGAUGGA	1089	TCCATCTG GGCTAGCTACAACGA TCCTGGCT	2791
4907	AGGAGCAG A UGGACAGC	1090	GCTGTCCA GGCTAGCTACAACGA CTGCTCCT	2792
4911	GCAGAUGG A CAGCGAUG	1091	CATCGCTG GGCTAGCTACAACGA CCATCTGC	2793
4914	GAUGGACA G CGAUGAGG	1092	CCTCATCG GGCTAGCTACAACGA TGTCCATC	2794
4917	GGACAGCG A UGAGGGA	1093	TCCCCTCA GGCTAGCTACAACGA CGCTGTCC	2795
4925	AUGAGGGG A CAUUUUCU	1094	AGAAAATG GGCTAGCTACAACGA CCCCTCAT	2796
4927	GAGGGGAC A UUUUCUGG	1095	CCAGAAAA GGCTAGCTACAACGA GTCCCCTC	2797
4936	UUUUCUGG A UUCUGGGA	1096	TCCCAGAA GGCTAGCTACAACGA CCAGAAAA	2798
4946	UCUGGGAG G CAAGAAAA	1097	TTTTCTTG GGCTAGCTACAACGA CTCCCAGA	2799
4957	AGAAAAGG A CAAAUAUC	1098	GATATTTG GGCTAGCTACAACGA CCTTTTCT	2800
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4975	UUUUUGGA A CUAAAGCA	1101	TGCTTTAG GGCTAGCTACAACGA TCCAAAAA	2803
4981	GAACUAAA G CAAAUUUU	1102	AAAATTTG GGCTAGCTACAACGA TTTAGTTC	2804
4985	UAAAGCAA A UUUUAGAC	1103	GTCTAAAA GGCTAGCTACAACGA TTGCTTTA	2805
4992	AAUUUUAG A CCUUUACC	1104	GGTAAAGG GGCTAGCTACAACGA CTAAAATT	2806
4998	AGACCUUU A CCUAUGGA	1105	TCCATAGG GGCTAGCTACAACGA AAAGGTCT	2807
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5008	CUAUGGAA G UGGUUCUA	1107	TAGAACCA GGCTAGCTACAACGA TTCCATAG	2809
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5016	GUGGUUCU A UGUCCAUU	1109	AATGGACA GGCTAGCTACAACGA AGAACCAC	2811
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5052	GAUUUGUA G CACUGAGG	1119	CCTCAGTG GGCTAGCTACAACGA TACAAATC	2821
5054	UUUGUAGC A CUGAGGGU	1120	ACCCTCAG GGCTAGCTACAACGA GCTACAAA	2822
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5064	UGAGGGUG G CACUCAAC	1122	GTTGAGTG GGCTAGCTACAACGA CACCCTCA	2824
5066	AGGGUGGC A CUCAACUC	1123	GAGTTGAG GGCTAGCTACAACGA GCCACCCT	2825
5071	GGCACUCA A CUCUGAGC	1124	GCTCAGAG GGCTAGCTACAACGA TGAGTGCC	2826
5078	AACUCUGA G CCCAUACU	1125	AGTATGGG GGCTAGCTACAACGA TCAGAGTT	2827
5082	CUGAGCCC A UACUUUUG	1126	CAAAAGTA GGCTAGCTACAACGA GGGCTCAG	2828
5084	GAGCCCAU A CUUUUGGC	1127	GCCAAAAG GGCTAGCTACAACGA ATGGGCTC	2829
5091	UACUUUUG G CUCCUCUA	1128	TAGAGGAG GGCTAGCTACAACGA CAAAAGTA	2830
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5105	CUAGUAAG A UGCACUGA	1130	TCAGTGCA GGCTAGCTACAACGA CTTACTAG	2832
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5121	AAAACUUA G CCAGAGUU	1134	AACTCTGG GGCTAGCTACAACGA TAAGTTTT	2836
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5132	AGAGUUAG G UUGUCUCC	1136	GGAGACAA GGCTAGCTACAACGA CTAACTCT	2838
5135	GUUAGGUU G UCUCCAGG	1137	CCTGGAGA GGCTAGCTACAACGA AACCTAAC	2839
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5334	GGAAAAAG G UCAAUAAG	1179	CTTATTGA GGCTAGCTACAACGA CTTTTTCC	2881
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5782	UUUAGGAU G CGCCUACU	1275	AGTAGGCG GGCTAGCTACAACGA ATCCTAAA	2977
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5871	GGGUCUAU G UAUUUAGG	1295	CCTAAATA GGCTAGCTACAACGA ATAGACCC	2997
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5909	AGUCAGAA G CUGGAGAG	1304	CTCTCCAG GGCTAGCTACAACGA TTCTGACT	3006
5918	CUGGAGAG G CAACAGUG	1305	CACTGTTG GGCTAGCTACAACGA CTCTCCAG	3007
5921	GAGAGGCA A CAGUGGAU	1306	ATCCACTG GGCTAGCTACAACGA TGCCTCTC	3008
5924	AGGCAACA G UGGAUUGC	1307	GCAATCCA GGCTAGCTACAACGA TGTTGCCT	3009
5928	AACAGUGG A UUGCUGCU	1308	AGCAGCAA GGCTAGCTACAACGA CCACTGTT	3010
5931	AGUGGAUU G CUGCUUCU	1309	AGAAGCAG GGCTAGCTACAACGA AATCCACT	3011
5934	GGAUUGCU G CUUCUUGG	1310	CCAAGAAG GGCTAGCTACAACGA AGCAATCC	3012
5951	GGAGAAGA G UAUGCUUC	1311	GAAGCATA GGCTAGCTACAACGA TCTTCTCC	3013
5953	AGAAGAGU A UGCUUCCU	1312	AGGAAGCA GGCTAGCTACAACGA ACTCTTCT	3014
5955	AAGAGUAU G CUUCCUUU	1313	AAAGGAAG GGCTAGCTACAACGA ATACTCTT	3015
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5969	UUUUAUCC A UGUAAUUU	1315	AAATTACA GGCTAGCTACAACGA GGATAAAA	3017
5971	UUAUCCAU G UAAUUUAA	1316	TTAAATTA GGCTAGCTACAACGA ATGGATAA	3018
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5979	GUAAUUUA A CUGUAGAA	1318	TTCTACAG GGCTAGCTACAACGA TAAATTAC	3020
5982	AUUUAACU G UAGAACCU	1319	AGGTTCTA GGCTAGCTACAACGA AGTTAAAT	3021
5987	ACUGUAGA A CCUGAGCU	1320	AGCTCAGG GGCTAGCTACAACGA TCTACAGT	3022
5993	GAACCUGA G CUCUAAGU	1321	ACTTAGAG GGCTAGCTACAACGA TCAGGTTC	3023
6000	AGCUCUAA G UAACCGAA	1322	TTCGGTTA GGCTAGCTACAACGA TTAGAGCT	3024
6003	UCUAAGUA A CCGAAGAA	1323	TTCTTCGG GGCTAGCTACAACGA TACTTAGA	3025
6011	ACCGAAGA A UGUAUGCC	1324	GGCATACA GGCTAGCTACAACGA TCTTCGGT	3026
6013	CGAAGAAU G UAUGCCUC	1325	GAGGCATA GGCTAGCTACAACGA ATTCTTCG	3027
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6017	GAAUGUAU G CCUCUGUU	1327	AACAGAGG GGCTAGCTACAACGA ATACATTC	3029
6023	AUGCCUCU G UUCUUAUG	1328	CATAAGAA GGCTAGCTACAACGA AGAGGCAT	3030
6029	CUGUUCUU A UGUGCCAC	1329	GTGGCACA GGCTAGCTACAACGA AAGAACAG	3031
6031	GUUCUUAU G UGCCACAU	1330	ATGTGGCA GGCTAGCTACAACGA ATAAGAAC	3032
6033	UCUUAUGU G CCACAUCC	1331	GGATGTGG GGCTAGCTACAACGA ACATAAGA	3033
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6061	CUCUCUGU A UGAAGAGA	1337	TCTCTTCA GGCTAGCTACAACGA ACAGAGAG	3039
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6080	GGACCGUC A UCAGCACA	1341	TGTGCTGA GGCTAGCTACAACGA GACGGTCC	3043
6084	CGUCAUCA G CACAUUCC	1342	GGAATGTG GGCTAGCTACAACGA TGATGACG	3044
6086	UCAUCAGC A CAUUCCCU	1343	AGGGAATG GGCTAGCTACAACGA GCTGATGA	3045
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6127	CGGCUUUU G UGGAAGAC	1352	GTCTTCCA GGCTAGCTACAACGA AAAAGCCG	3054
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6254	ACACAUAC G CAAACCAC	1374	GTGGTTTG GGCTAGCTACAACGA GTATGTGT	3076
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6271	CUGUGACA G CUGGCAAU	1379	ATTGCCAG GGCTAGCTACAACGA TGTCACAG	3081
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6945	AAGGAGGA G UGCAUCUU	1523	AAGATGCA GGCTAGCTACAACGA TCCTCCTT	3225
6947	GGAGGAGU G CAUCUUUG	1524	CAAAGATG GGCTAGCTACAACGA ACTCCTCC	3226
6949	AGGAGUGC A UCUUUGGC	1525	GCCAAAGA GGCTAGCTACAACGA GCACTCCT	3227
6956	CAUCUUUG G CCGACAGU	1526	ACTGTCGG GGCTAGCTACAACGA CAAAGATG	3228
6960	UUUGGCCG A CAGUGGUG	1527	CACCACTG GGCTAGCTACAACGA CGGCCAAA	3229
6963	GGCCGACA G UGGUGUAA	1528	TTACACCA GGCTAGCTACAACGA TGTCGGCC	3230
6966	CGACAGUG G UGUAACUG	1529	CAGTTACA GGCTAGCTACAACGA CACTGTCG	3231
6968	ACAGUGGU G UAACUGUG	1530	CACAGTTA GGCTAGCTACAACGA ACCACTGT	3232
6971	GUGGUGUA A CUGUGUGU	1531	ACACACAG GGCTAGCTACAACGA TACACCAC	3233
6974	GUGUAACU G UGUGUGUG	1532	CACACACA GGCTAGCTACAACGA AGTTACAC	3234
6976	GUAACUGU G UGUGUGUG	1533	CACACACA GGCTAGCTACAACGA ACAGTTAC	3235
6978	AACUGUGU G UGUGUGUG	1534	CACACACA GGCTAGCTACAACGA ACACAGTT	3236
6980	CUGUGUGU G UGUGUGUG	1535	CACACACA GGCTAGCTACAACGA ACACACAG	3237
6982	GUGUGUGU G UGUGUGUG	1536	CACACACA GGCTAGCTACAACGA ACACACAC	3238
6984	GUGUGUGU G UGUGUGUG	1537	CACACACA GGCTAGCTACAACGA ACACACAC	3239
6986	GUGUGUGU G UGUGUGUG	1538	CACACACA GGCTAGCTACAACGA ACACACAC	3240
6988	GUGUGUGU G UGUGUGUG	1539	CACACACA GGCTAGCTACAACGA ACACACAC	3241
6990	GUGUGUGU G UGUGUGUG	1540	CACACACA GGCTAGCTACAACGA ACACACAC	3242
6992	GUGUGUGU G UGUGUGUG	1541	CACACACA GGCTAGCTACAACGA ACACACAC	3243
6994	GUGUGUGU G UGUGUGUG	1542	CACACACA GGCTAGCTACAACGA ACACACAC	3244
6996	GUGUGUGU G UGUGUGUG	1543	CACACACA GGCTAGCTACAACGA ACACACAC	3245
6998	GUGUGUGU G UGUGUGUG	1544	CACACACA GGCTAGCTACAACGA ACACACAC	3246
7000	GUGUGUGU G UGUGUGUG	1545	CACACACA GGCTAGCTACAACGA ACACACAC	3247
7002	GUGUGUGU G UGUGUGUG	1546	CACACACA GGCTAGCTACAACGA ACACACAC	3248
7004	GUGUGUGU G UGUGUGUG	1547	CACACACA GGCTAGCTACAACGA ACACACAC	3249
7006	GUGUGUGU G UGUGUGUG	1548	CACACACA GGCTAGCTACAACGA ACACACAC	3250
7008	GUGUGUGU G UGUGUGGG	1549	CCCACACA GGCTAGCTACAACGA ACACACAC	3251
7010	GUGUGUGU G UGUGGGUG	1550	CACCCACA GGCTAGCTACAACGA ACACACAC	3252
7012	GUGUGUGU G UGGGUGUG	1551	CACACCCA GGCTAGCTACAACGA ACACACAC	3253
7016	GUGUGUGG G UGUGGGUG	1552	CACCCACA GGCTAGCTACAACGA CCACACAC	3254
7018	GUGUGGGU G UGGGUGUA	1553	TACACCCA GGCTAGCTACAACGA ACCCACAC	3255
7022	GGGUGUGG G UGUAUGUG	1554	CACATACA GGCTAGCTACAACGA CCACACCC	3256
7024	GUGUGGGU G UAUGUGUG	1555	CACACATA GGCTAGCTACAACGA ACCCACAC	3257
7026	GUGGGUGU A UGUGUGUU	1556	AACACACA GGCTAGCTACAACGA ACACCCAC	3258

7028	GGGUGUAU G UGUGUUUU	1557	AAAACACA GGCTAGCTACAACGA ATACACCC	3259
7030	GUGUAUGU G UGUUUUGU	1558	ACAAAACA GGCTAGCTACAACGA ACATACAC	3260
7032	GUAUGUGU G UUUUGUGC	1559	GCACAAAA GGCTAGCTACAACGA ACACATAC	3261
7037	UGUGUUUU G UGCAUAAC	1560	GTTATGCA GGCTAGCTACAACGA AAAACACA	3262
7039	UGUUUUGU G CAUAACUA	1561	TAGTTATG GGCTAGCTACAACGA ACAAAACA	3263
7041	UUUUGUGC A UAACUAUU	1562	AATAGTTA GGCTAGCTACAACGA GCACAAAA	3264
7044	UGUGCAUA A CUAUUUAA	1563	TTAAATAG GGCTAGCTACAACGA TATGCACA	3265
7047	GCAUAACU A UUUAAGGA	1564	TCCTTAAA GGCTAGCTACAACGA AGTTATGC	3266
7057	UUAAGGAA A CUGGAAUU	1565	AATTCCAG GGCTAGCTACAACGA TTCCTTAA	3267
7063	AAACUGGA A UUUUAAAG	1566	CTTTAAAA GGCTAGCTACAACGA TCCAGTTT	3268
7071	AUUUUAAA G UUACUUUU	1567	AAAAGTAA GGCTAGCTACAACGA TTTAAAAT	3269
7074	UUAAAGUU A CUUUUAUA	1568	TATAAAAG GGCTAGCTACAACGA AACTTTAA	3270
7080	UUACUUUU A UACAAACC	1569	GGTTTGTA GGCTAGCTACAACGA AAAAGTAA	3271
7082	ACUUUUAU A CAAACCAA	1570	TTGGTTTG GGCTAGCTACAACGA ATAAAAGT	3272
7086	UUAUACAA A CCAAGAAU	1571	ATTCTTGG GGCTAGCTACAACGA TTGTATAA	3273
7093	AACCAAGA A UAUAUGCU	1572	AGCATATA GGCTAGCTACAACGA TCTTGGTT	3274
7095	CCAAGAAU A UAUGCUAC	1573	GTAGCATA GGCTAGCTACAACGA ATTCTTGG	3275
7097	AAGAAUAU A UGCUACAG	1574	CTGTAGCA GGCTAGCTACAACGA ATATTCTT	3276
7099	GAAUAUAU G CUACAGAU	1575	ATCTGTAG GGCTAGCTACAACGA ATATATTC	3277
7102	UAUAUGCU A CAGAUAUA	1576	TATATCTG GGCTAGCTACAACGA AGCATATA	3278
7106	UGCUACAG A UAUAAGAC	1577	GTCTTATA GGCTAGCTACAACGA CTGTAGCA	3279
7108	CUACAGAU A UAAGACAG	1578	CTGTCTTA GGCTAGCTACAACGA ATCTGTAG	3280
7113	GAUAUAAG A CAGACAUG	1579	CATGTCTG GGCTAGCTACAACGA CTTATATC	3281
7117	UAAGACAG A CAUGGUUU	1580	AAACCATG GGCTAGCTACAACGA CTGTCTTA	3282
7119	AGACAGAC A UGGUUUGG	1581	CCAAACCA GGCTAGCTACAACGA GTCTGTCT	3283
7122	CAGACAUG G UUUGGUCC	1582	GGACCAAA GGCTAGCTACAACGA CATGTCTG	3284
7127	AUGGUUUG G UCCUAUAU	1583	ATATAGGA GGCTAGCTACAACGA CAAACCAT	3285
7132	UUGGUCCU A UAUUUCUA	1584	TAGAAATA GGCTAGCTACAACGA AGGACCAA	3286
7134	GGUCCUAU A UUUCUAGU	1585	ACTAGAAA GGCTAGCTACAACGA ATAGGACC	3287
7141	UAUUUCUA G UCAUGAUG	1586	CATCATGA GGCTAGCTACAACGA TAGAAATA	3288
7144	UUCUAGUC A UGAUGAAU	1587	ATTCATCA GGCTAGCTACAACGA GACTAGAA	3289
7147	UAGUCAUG A UGAAUGUA	1588	TACATTCA GGCTAGCTACAACGA CATGACTA	3290
7151	CAUGAUGA A UGUAUUUU	1589	AAAATACA GGCTAGCTACAACGA TCATCATG	3291
7153	UGAUGAAU G UAUUUUGU	1590	ACAAAATA GGCTAGCTACAACGA ATTCATCA	3292
7155	AUGAAUGU A UUUUGUAU	1591	ATACAAAA GGCTAGCTACAACGA ACATTCAT	3293
7160	UGUAUUUU G UAUACCAU	1592	ATGGTATA GGCTAGCTACAACGA AAAATACA	3294
7162	UAUUUUGU A UACCAUCU	1593	AGATGGTA GGCTAGCTACAACGA ACAAAATA	3295
7164	UUUUGUAU A CCAUCUUC	1594	GAAGATGG GGCTAGCTACAACGA ATACAAAA	3296
7167	UGUAUACC A UCUUCAUA	1595	TATGAAGA GGCTAGCTACAACGA GGTATACA	3297
7173	CCAUCUUC A UAUAAUAU	1596	ATATTATA GGCTAGCTACAACGA GAAGATGG	3298
7175	AUCUUCAU A UAAUAUAC	1597	GTATATTA GGCTAGCTACAACGA ATGAAGAT	3299
7178	UUCAUAUA A UAUACUUA	1598	TAAGTATA GGCTAGCTACAACGA TATATGAA	3300
7180	CAUAUAAU A UACUUAAA	1599	TTTAAGTA GGCTAGCTACAACGA ATTATATG	3301
7182	UAUAAUAU A CUUAAAAA	1600	TTTTTAAG GGCTAGCTACAACGA ATATTATA	3302
7190	ACUUAAAA A UAUUUCUU	1601	AAGAAATA GGCTAGCTACAACGA TTTTAAGT	3303
7192	UUAAAAAU A UUUCUUAA	1602	TTAAGAAA GGCTAGCTACAACGA ATTTTTAA	3304
7200	AUUUCUUA A UUGGGAUU	1603	AATCCCAA GGCTAGCTACAACGA TAAGAAAT	3305
7206	UAAUUGGG A UUUGUAAU	1604	ATTACAAA GGCTAGCTACAACGA CCCAATTA	3306
7210	UGGGAUUU G UAAUCGUA	1605	TACGATTA GGCTAGCTACAACGA AAATCCCA	3307
7213	GAUUUGUA A UCGUACCA	1606	TGGTACGA GGCTAGCTACAACGA TACAAATC	3308
7216	UUGUAAUC G UACCAACU	1607	AGTTGGTA GGCTAGCTACAACGA GATTACAA	3309
7218	GUAAUCGU A CCAACUUA	1608	TAAGTTGG GGCTAGCTACAACGA ACGATTAC	3310

7222	UCGUACCA A CUUAAUUG	1609	CAATTAAG GGCTAGCTACAACGA TGGTACGA	3311
7227	CCAACUUA A UUGAUAAA	1610	TTTATCAA GGCTAGCTACAACGA TAAGTTGG	3312
7231	CUUAAUUG A UAAACUUG	1611	CAAGTTTA GGCTAGCTACAACGA CAATTAAG	3313
7235	AUUGAUAA A CUUGGCAA	1612	TTGCCAAG GGCTAGCTACAACGA TTATCAAT	3314
7240	UAAACUUG G CAACUGCU	1613	AGCAGTTG GGCTAGCTACAACGA CAAGTTTA	3315
7243	ACUUGGCA A CUGCUUUU	1614	AAAAGCAG GGCTAGCTACAACGA TGCCAAGT	3316
7246	UGGCAACU G CUUUUAUG	1615	CATAAAAG GGCTAGCTACAACGA AGTTGCCA	3317
7252	CUGCUUUU A UGUUCUGU	1616	ACAGAACA GGCTAGCTACAACGA AAAAGCAG	3318
7254	GCUUUUAU G UUCUGUCU	1617	AGACAGAA GGCTAGCTACAACGA ATAAAAGC	3319
7259	UAUGUUCU G UCUCCUUC	1618	GAAGGAGA GGCTAGCTACAACGA AGAACATA	3320
7269	CUCCUUCC A UAAAUUUU	1619	AAAATTTA GGCTAGCTACAACGA GGAAGGAG	3321
7273	UUCCAUAA A UUUUUCAA	1620	TTGAAAAA GGCTAGCTACAACGA TTATGGAA	3322
7283	UUUUCAAA A UACUAAUU	1621	AATTAGTA GGCTAGCTACAACGA TTTGAAAA	3323
7285	UUCAAAAU A CUAAUUCA	1622	TGAATTAG GGCTAGCTACAACGA ATTTTGAA	3324
7289	AAAUACUA A UUCAACAA	1623	TTGTTGAA GGCTAGCTACAACGA TAGTATTT	3325
7294	CUAAUUCA A CAAAGAAA	1624	TTTCTTTG GGCTAGCTACAACGA TGAATTAG	3326
7305	AAGAAAAA G CUCUUUUU	1625	AAAAAGAG GGCTAGCTACAACGA TTTTTCTT	3327
7323	UUCCUAAA A UAAACUCA	1626	TGAGTTTA GGCTAGCTACAACGA TTTAGGAA	3328
7327	UAAAAUAA A CUCAAAUU	1627	AATTTGAG GGCTAGCTACAACGA TTATTTTA	3329
7333	AAACUCAA A UUUAUCCU	1628	AGGATAAA GGCTAGCTACAACGA TTGAGTTT	3330
7337	UCAAAUUU A UCCUUGUU	1629	AACAAGGA GGCTAGCTACAACGA AAATTTGA	3331
7343	UUAUCCUU G UUUAGAGC	1630	GCTCTAAA GGCTAGCTACAACGA AAGGATAA	3332
7350	UGUUUAGA G CAGAGAAA	1631	TTTCTCTG GGCTAGCTACAACGA TCTAAACA	3333
7360	AGAGAAAA A UUAAGAAA	1632	TTTCTTAA GGCTAGCTACAACGA TTTTCTCT	3334
7370	UAAGAAAA A CUUUGAAA	1633	TTTCAAAG GGCTAGCTACAACGA TTTTCTTA	3335
7378	ACUUUGAA A UGGUCUCA	1634	TGAGACCA GGCTAGCTACAACGA TTCAAAGT	3336
7381	UUGAAAUG G UCUCAAAA	1635	TTTTGAGA GGCTAGCTACAACGA CATTTCAA	3337
7391	CUCAAAAA A UUGCUAAA	1636	TTTAGCAA GGCTAGCTACAACGA TTTTTGAG	3338
7394	AAAAAAUU G CUAAAUAU	1637	ATATTTAG GGCTAGCTACAACGA AATTTTTT	3339
7399	AUUGCUAA A UAUUUUCA	1638	TGAAAATA GGCTAGCTACAACGA TTAGCAAT	3340
7401	UGCUAAAU A UUUUCAAU	1639	ATTGAAAA GGCTAGCTACAACGA ATTTAGCA	3341
7408	UAUUUUCA A UGGAAAAC	1640	GTTTTCCA GGCTAGCTACAACGA TGAAAATA	3342
7415	AAUGGAAA A CUAAAUGU	1641	ACATTTAG GGCTAGCTACAACGA TTTCCATT	3343
7420	AAAACUAA A UGUUAGUU	1642	AACTAACA GGCTAGCTACAACGA TTAGTTTT	3344
7422	AACUAAAU G UUAGUUUA	1643	TAAACTAA GGCTAGCTACAACGA ATTTAGTT	3345
7426	AAAUGUUA G UUUAGCUG	1644	CAGCTAAA GGCTAGCTACAACGA TAACATTT	3346
7431	UUAGUUUA G CUGAUUGU	1645	ACAATCAG GGCTAGCTACAACGA TAAACTAA	3347
7435	UUUAGCUG A UUGUAUGG	1646	CCATACAA GGCTAGCTACAACGA CAGCTAAA	3348
7438	AGCUGAUU G UAUGGGGU	1647	ACCCCATA GGCTAGCTACAACGA AATCAGCT	3349
7440	CUGAUUGU A UGGGGUUU	1648	AAACCCCA GGCTAGCTACAACGA ACAATCAG	3350
7445	UGUAUGGG G UUUUCGAA	1649	TTCGAAAA GGCTAGCTACAACGA CCCATACA	3351
7453	GUUUUCGA A CCUUUCAC	1650	GTGAAAGG GGCTAGCTACAACGA TCGAAAAC	3352
7460	AACCUUUC A CUUUUUGU	1651	ACAAAAAG GGCTAGCTACAACGA GAAAGGTT	3353
7467	CACUUUUU G UUUGUUUU	1652	AAAACAAA GGCTAGCTACAACGA AAAAAGTG	3354
7471	UUUUGUUU G UUUUACCU	1653	AGGTAAAA GGCTAGCTACAACGA AAACAAAA	3355
7476	UUUGUUUU A CCUAUUUC	1654	GAAATAGG GGCTAGCTACAACGA AAAACAAA	3356
7480	UUUUACCU A UUUCACAA	1655	TTGTGAAA GGCTAGCTACAACGA AGGTAAAA	3357
7485	CCUAUUUC A CAACUGUG	1656	CACAGTTG GGCTAGCTACAACGA GAAATAGG	3358
7488	AUUUCACA A CUGUGUAA	1657	TTACACAG GGCTAGCTACAACGA TGTGAAAT	3359
7491	UCACAACU G UGUAAAUU	1658	AATTTACA GGCTAGCTACAACGA AGTTGTGA	3360
7493	ACAACUGU G UAAAUUGC	1659	GCAATTTA GGCTAGCTACAACGA ACAGTTGT	3361
7497	CUGUGUAA A UUGCCAAU	1660	ATTGGCAA GGCTAGCTACAACGA TTACACAG	3362

7500	UGUAAAUU G CCAAUAAU	1661	ATTATTGG GGCTAGCTACAACGA AATTTACA	3363
7504	AAUUGCCA A UAAUUCCU	1662	AGGAATTA GGCTAGCTACAACGA TGGCAATT	3364
7507	UGCCAAUA A UUCCUGUC	1663	GACAGGAA GGCTAGCTACAACGA TATTGGCA	3365
7513	UAAUUCCU G UCCAUGAA	1664	TTCATGGA GGCTAGCTACAACGA AGGAATTA	3366
7517	UCCUGUCC A UGAAAAUG	1665	CATTTTCA GGCTAGCTACAACGA GGACAGGA	3367
7523	CCAUGAAA A UGCAAAUU	1666	AATTTGCA GGCTAGCTACAACGA TTTCATGG	3368
7525	AUGAAAAU G CAAAUUAU	1667	ATAATTTG GGCTAGCTACAACGA ATTTTCAT	3369
7529	AAAUGCAA A UUAUCCAG	1668	CTGGATAA GGCTAGCTACAACGA TTGCATTT	3370
7532	UGCAAAUU A UCCAGUGU	1669	ACACTGGA GGCTAGCTACAACGA AATTTGCA	3371
7537	AUUAUCCA G UGUAGAUA	1670	TATCTACA GGCTAGCTACAACGA TGGATAAT	3372
7539	UAUCCAGU G UAGAUAUA	1671	TATATCTA GGCTAGCTACAACGA ACTGGATA	3373
7543	CAGUGUAG A UAUAUUUG	1672	CAAATATA GGCTAGCTACAACGA CTACACTG	3374
7545	GUGUAGAU A UAUUUGAC	1673	GTCAAATA GGCTAGCTACAACGA ATCTACAC	3375
7547	GUAGAUAU A UUUGACCA	1674	TGGTCAAA GGCTAGCTACAACGA ATATCTAC	3376
7552	UAUAUUUG A CCAUCACC	1675	GGTGATGG GGCTAGCTACAACGA CAAATATA	3377
7555	AUUUGACC A UCACCCUA	1676	TAGGGTGA GGCTAGCTACAACGA GGTCAAAT	3378
7558	UGACCAUC A CCCUAUGG	1677	CCATAGGG GGCTAGCTACAACGA GATGGTCA	3379
7563	AUCACCCU A UGGAUAUU	1678	AATATCCA GGCTAGCTACAACGA AGGGTGAT	3380
7567	CCCUAUGG A UAUUGGCU	1679	AGCCAATA GGCTAGCTACAACGA CCATAGGG	3381
7569	CUAUGGAU A UUGGCUAG	1680	CTAGCCAA GGCTAGCTACAACGA ATCCATAG	3382
7573	GGAUAUUG G CUAGUUUU	1681	AAAACTAG GGCTAGCTACAACGA CAATATCC	3383
7577	AUUGGCUA G UUUUGCCU	1682	AGGCAAAA GGCTAGCTACAACGA TAGCCAAT	3384
7582	CUAGUUUU G CCUUUAUU	1683	AATAAAGG GGCTAGCTACAACGA AAAACTAG	3385
7588	UUGCCUUU A UUAAGCAA	1684	TTGCTTAA GGCTAGCTACAACGA AAAGGCAA	3386
7593	UUUAUUAA G CAAAUUCA	1685	TGAATTTG GGCTAGCTACAACGA TTAATAAA	3387
7597	UUAAGCAA A UUCAUUUC	1686	GAAATGAA GGCTAGCTACAACGA TTGCTTAA	3388
7601	GCAAAUUC A UUUCAGCC	1687	GGCTGAAA GGCTAGCTACAACGA GAATTTGC	3389
7607	UCAUUUCA G CCUGAAUG	1688	CATTCAGG GGCTAGCTACAACGA TGAAATGA	3390
7613	CAGCCUGA A UGUCUGCC	1689	GGCAGACA GGCTAGCTACAACGA TCAGGCTG	3391
7615	GCCUGAAU G UCUGCCUA	1690	TAGGCAGA GGCTAGCTACAACGA ATTCAGGC	3392
7619	GAAUGUCU G CCUAUAUA	1691	TATATAGG GGCTAGCTACAACGA AGACATTC	3393
7623	GUCUGCCU A UAUAUUCU	1692	AGAATATA GGCTAGCTACAACGA AGGCAGAC	3394
7625	CUGCCUAU A UAUUCUCU	1693	AGAGAATA GGCTAGCTACAACGA ATAGGCAG	3395
7627	GCCUAUAU A UUCUCUGC	1694	GCAGAGAA GGCTAGCTACAACGA ATATAGGC	3396
7634	UAUUCUCU G CUCUUUGU	1695	ACAAAGAG GGCTAGCTACAACGA AGAGAATA	3397
7641	UGCUCUUU G UAUUCUCC	1696	GGAGAATA GGCTAGCTACAACGA AAAGAGCA	3398
7643	CUCUUUGU A UUCUCCUU	1697	AAGGAGAA GGCTAGCTACAACGA ACAAAGAG	3399
7655	UCCUUUGA A CCCGUUAA	1698	TTAACGGG GGCTAGCTACAACGA TCAAAGGA	3400
7659	UUGAACCC G UUAAAACA	1699	TGTTTTAA GGCTAGCTACAACGA GGGTTCAA	3401
7665	CCGUUAAA A CAUCCUGU	1700	ACAGGATG GGCTAGCTACAACGA TTTAACGG	3402
7667	GUUAAAAC A UCCUGUGG	1701	CCACAGGA GGCTAGCTACAACGA GTTTTAAC	3403
7672	AACAUCCU G UGGCACUC	1702	GAGTGCCA GGCTAGCTACAACGA AGGATGTT	3404

Input Sequence = HSFLT. Cut Site = R/Y
Arm Length = 8. Core Sequence = GGCTAGCTACAACGA
HSFLT (Human flt mRNA for receptor-related tyrosine kinase.; Acc# X51602; 7680 bp)

Table VI: Human KDR DNAzyme and Substrate sequence

Pos	Substrate	Seq ID No	DNAzyme	Seq ID No
14	GUCCCGGG A CCCCGGGA	3405	TCCCGGGG GGCTAGCTACAACGA CCCGGGAC	4691
25	CCGGGAGA G CGGUCAGU	3406	ACTGACCG GGCTAGCTACAACGA TCTCCCGG	4692
28	GGAGAGCG G UCAGUGUG	3407	CACACTGA GGCTAGCTACAACGA CGCTCTCC	4693
32	AGCGGUCA G UGUGUGGU	3408	ACCACACA GGCTAGCTACAACGA TGACCGCT	4694
34	CGGUCAGU G UGUGGUCG	3409	CGACCACA GGCTAGCTACAACGA ACTGACCG	4695
36	GUCAGUGU G UGGUCGCU	3410	AGCGACCA GGCTAGCTACAACGA ACACTGAC	4696
39	AGUGUGUG G UCGCUGCG	3411	CGCAGCGA GGCTAGCTACAACGA CACACACT	4697
42	GUGUGGUC G CUGCGUUU	3412	AAACGCAG GGCTAGCTACAACGA GACCACAC	4698
45	UGGUCGCU G CGUUUCCU	3413	AGGAAACG GGCTAGCTACAACGA AGCGACCA	4699
47	GUCGCUGC G UUUCCUCU	3414	AGAGGAAA GGCTAGCTACAACGA GCAGCGAC	4700
56	UUUCCUCU G CCUGCGCC	3415	GGCGCAGG GGCTAGCTACAACGA AGAGGAAA	4701
60	CUCUGCCU G CGCCGGGC	3416	GCCCGGCG GGCTAGCTACAACGA AGGCAGAG	4702
62	CUGCCUGC G CCGGGCAU	3417	ATGCCCGG GGCTAGCTACAACGA GCAGGCAG	4703
67	UGCGCCGG G CAUCACUU	3418	AAGTGATG GGCTAGCTACAACGA CCGGCGCA	4704
69	CGCCGGGC A UCACUUGC	3419	GCAAGTGA GGCTAGCTACAACGA GCCCGGCG	4705
72	CGGGCAUC A CUUGCGCG	3420	CGCGCAAG GGCTAGCTACAACGA GATGCCCG	4706
76	[illegible]AUCACUU G CGCGCCGC	3421	GCGGCGCG GGCTAGCTACAACGA AAGTGATG	4707
78	UCACUUGC G CGCCGCAG	3422	CTGCGGCG GGCTAGCTACAACGA GCAAGTGA	4708
80	ACUUGCGC G CCGCAGAA	3423	TTCTGCGG GGCTAGCTACAACGA GCGCAAGT	4709
83	UGCGCGCC G CAGAAAGU	3424	ACTTTCTG GGCTAGCTACAACGA GGCGCGCA	4710
90	CGCAGAAA G UCCGUCUG	3425	CAGACGGA GGCTAGCTACAACGA TTTCTGCG	4711
94	GAAAGUCC G UCUGGCAG	3426	CTGCCAGA GGCTAGCTACAACGA GGACTTTC	4712
99	UCCGUCUG G CAGCCUGG	3427	CCAGGCTG GGCTAGCTACAACGA CAGACGGA	4713
102	GUCUGGCA G CCUGGAUA	3428	TATCCAGG GGCTAGCTACAACGA TGCCAGAC	4714
108	CAGCCUGG A UAUCCUCU	3429	AGAGGATA GGCTAGCTACAACGA CCAGGCTG	4715
110	GCCUGGAU A UCCUCUCC	3430	GGAGAGGA GGCTAGCTACAACGA ATCCAGGC	4716
120	CCUCUCCU A CCGGCACC	3431	GGTGCCGG GGCTAGCTACAACGA AGGAGAGG	4717
124	UCCUACCG G CACCCGCA	3432	TGCGGGTG GGCTAGCTACAACGA CGGTAGGA	4718
126	CUACCGGC A CCCGCAGA	3433	TCTGCGGG GGCTAGCTACAACGA GCCGGTAG	4719
130	CGGCACCC G CAGACGCC	3434	GGCGTCTG GGCTAGCTACAACGA GGGTGCCG	4720
134	ACCCGCAG A CGCCCCUG	3435	CAGGGGCG GGCTAGCTACAACGA CTGCGGGT	4721
136	CCGCAGAC G CCCCUGCA	3436	TGCAGGGG GGCTAGCTACAACGA GTCTGCGG	4722
142	ACGCCCCU G CAGCCGCC	3437	GGCGGCTG GGCTAGCTACAACGA AGGGGCGT	4723
145	CCCCUGCA G CCGCCGGU	3438	ACCGGCGG GGCTAGCTACAACGA TGCAGGGG	4724
148	CUGCAGCC G CCGGUCGG	3439	CCGACCGG GGCTAGCTACAACGA GGCTGCAG	4725
152	AGCCGCCG G UCGGCGCC	3440	GGCGCCGA GGCTAGCTACAACGA CGGCGGCT	4726
156	GCCGGUCG G CGCCCGGG	3441	CCCGGGCG GGCTAGCTACAACGA CGACCGGC	4727
158	CGGUCGGC G CCCGGGCU	3442	AGCCCGGG GGCTAGCTACAACGA GCCGACCG	4728
164	GCGCCCGG G CUCCCUAG	3443	CTAGGGAG GGCTAGCTACAACGA CCGGGCGC	4729
172	GCUCCCUA G CCCUGUGC	3444	GCACAGGG GGCTAGCTACAACGA TAGGGAGC	4730
177	CUAGCCCU G UGCGCUCA	3445	TGAGCGCA GGCTAGCTACAACGA AGGGCTAG	4731
179	AGCCCUGU G CGCUCAAC	3446	GTTGAGCG GGCTAGCTACAACGA ACAGGGCT	4732
181	CCCUGUGC G CUCAACUG	3447	CAGTTGAG GGCTAGCTACAACGA GCACAGGG	4733
186	UGCGCUCA A CUGUCCUG	3448	CAGGACAG GGCTAGCTACAACGA TGAGCGCA	4734
189	GCUCAACU G UCCUGCGC	3449	GCGCAGGA GGCTAGCTACAACGA AGTTGAGC	4735
194	ACUGUCCU G CGCUGCGG	3450	CCGCAGCG GGCTAGCTACAACGA AGGACAGT	4736
196	UGUCCUGC G CUGCGGGG	3451	CCCCGCAG GGCTAGCTACAACGA GCAGGACA	4737
199	CCUGCGCU G CGGGGUGC	3452	GCACCCCG GGCTAGCTACAACGA AGCGCAGG	4738
204	GCUGCGGG G UGCCGCGA	3453	TCGCGGCA GGCTAGCTACAACGA CCCGCAGC	4739

206	UGCGGGGU G CCGCGAGU	3454	ACTCGCGG GGCTAGCTACAACGA ACCCCGCA	4740
209	GGGGUGCC G CGAGUUCC	3455	GGAACTCG GGCTAGCTACAACGA GGCACCCC	4741
213	UGCCGCGA G UUCCACCU	3456	AGGTGGAA GGCTAGCTACAACGA TCGCGGCA	4742
218	CGAGUUCC A CCUCCGCG	3457	CGCGGAGG GGCTAGCTACAACGA GGAACTCG	4743
224	CCACCUCC G CGCCUCCU	3458	AGGAGGCG GGCTAGCTACAACGA GGAGGTGG	4744
226	ACCUCCGC G CCUCCUUC	3459	GAAGGAGG GGCTAGCTACAACGA GCGGAGGT	4745
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244	CUAGACAG G CGCUGGGA	3461	TCCCAGCG GGCTAGCTACAACGA CTGTCTAG	4747
246	AGACAGGC G CUGGGAGA	3462	TCTCCCAG GGCTAGCTACAACGA GCCTGTCT	4748
259	GAGAAAGA A CCGGCUCC	3463	GGAGCCGG GGCTAGCTACAACGA TCTTTCTC	4749
263	AAGAACCG G CUCCCGAG	3464	CTCGGGAG GGCTAGCTACAACGA CGGTTCTT	4750
271	GCUCCCGA G UUCUGGGC	3465	GCCCAGAA GGCTAGCTACAACGA TCGGGAGC	4751
278	AGUUCUGG G CAUUUCGC	3466	GCGAAATG GGCTAGCTACAACGA CCAGAACT	4752
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285	GGCAUUUC G CCCGGCUC	3468	GAGCCGGG GGCTAGCTACAACGA GAAATGCC	4754
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299	CUCGAGGU G CAGGAUGC	3471	GCATCCTG GGCTAGCTACAACGA ACCTCGAG	4757
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321	AAGGUGCU G CUGGCCGU	3477	ACGGCCAG GGCTAGCTACAACGA AGCACCTT	4763
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328	UGCUGGCC G UCGCCCUG	3479	CAGGGCGA GGCTAGCTACAACGA GGCCAGCA	4765
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336	GUCGCCCU G UGGCUCUG	3481	CAGAGCCA GGCTAGCTACAACGA AGGGCGAC	4767
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421	AAAAAGAC A UACUUACA	3500	TGTAAGTA GGCTAGCTACAACGA GTCTTTTT	4786
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442	AGGCUAAU A CAACUCUU	3506	AAGAGTTG GGCTAGCTACAACGA ATTAGCCT	4792

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457	UUCAAAUU A CUUGCAGG	3509	CCTGCAAG GGCTAGCTACAACGA AATTTGAA	4795
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1172	AUUUUUGA G CACCUUAA	3670	TTAAGGTG GGCTAGCTACAACGA TCAAAAAT	4956
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1180	GCACCUUA A CUAUAGAU	3672	ATCTATAG GGCTAGCTACAACGA TAAGGTGC	4958
1183	CCUUAACU A UAGAUGGU	3673	ACCATCTA GGCTAGCTACAACGA AGTTAAGG	4959
1187	AACUAUAG A UGGUGUAA	3674	TTACACCA GGCTAGCTACAACGA CTATAGTT	4960
1190	UAUAGAUG G UGUAACCC	3675	GGGTTACA GGCTAGCTACAACGA CATCTATA	4961
1192	UAGAUGGU G UAACCCGG	3676	CCGGGTTA GGCTAGCTACAACGA ACCATCTA	4962
1195	AUGGUGUA A CCCGGAGU	3677	ACTCCGGG GGCTAGCTACAACGA TACACCAT	4963
1202	AACCCGGA G UGACCAAG	3678	CTTGGTCA GGCTAGCTACAACGA TCCGGGTT	4964
1205	CCGGAGUG A CCAAGGAU	3679	ATCCTTGG GGCTAGCTACAACGA CACTCCGG	4965
1212	GACCAAGG A UUGUACAC	3680	GTGTACAA GGCTAGCTACAACGA CCTTGGTC	4966
1215	CAAGGAUU G UACACCUG	3681	CAGGTGTA GGCTAGCTACAACGA AATCCTTG	4967
1217	AGGAUUGU A CACCUGUG	3682	CACAGGTG GGCTAGCTACAACGA ACAATCCT	4968
1219	GAUUGUAC A CCUGUGCA	3683	TGCACAGG GGCTAGCTACAACGA GTACAATC	4969
1223	GUACACCU G UGCAGCAU	3684	ATGCTGCA GGCTAGCTACAACGA AGGTGTAC	4970
1225	ACACCUGU G CAGCAUCC	3685	GGATGCTG GGCTAGCTACAACGA ACAGGTGT	4971
1228	CCUGUGCA G CAUCCAGU	3686	ACTGGATG GGCTAGCTACAACGA TGCACAGG	4972
1230	UGUGCAGC A UCCAGUGG	3687	CCACTGGA GGCTAGCTACAACGA GCTGCACA	4973
1235	AGCAUCCA G UGGGCUGA	3688	TCAGCCCA GGCTAGCTACAACGA TGGATGCT	4974
1239	UCCAGUGG G CUGAUGAC	3689	GTCATCAG GGCTAGCTACAACGA CCACTGGA	4975
1243	GUGGGCUG A UGACCAAG	3690	CTTGGTCA GGCTAGCTACAACGA CAGCCCAC	4976
1246	GGCUGAUG A CCAAGAAG	3691	CTTCTTGG GGCTAGCTACAACGA CATCAGCC	4977
1256	CAAGAAGA A CAGCACAU	3692	ATGTGCTG GGCTAGCTACAACGA TCTTCTTG	4978
1259	GAAGAACA G CACAUUUG	3693	CAAATGTG GGCTAGCTACAACGA TGTTCTTC	4979
1261	AGAACAGC A CAUUUGUC	3694	GACAAATG GGCTAGCTACAACGA GCTGTTCT	4980
1263	AACAGCAC A UUUGUCAG	3695	CTGACAAA GGCTAGCTACAACGA GTGCTGTT	4981
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1273	UUGUCAGG G UCCAUGAA	.3697	TTCATGGA GGCTAGCTACAACGA CCTGACAA	4983
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1327	UGGUGGAA G CCACGGUG	3707	CACCGTGG GGCTAGCTACAACGA TTCCACCA	4993
1330	UGGAAGCC A CGGUGGGG	3708	CCCCACCG GGCTAGCTACAACGA GGCTTCCA	4994
1333	AAGCCACG G UGGGGGAG	3709	CTCCCCCA GGCTAGCTACAACGA CGTGGCTT	4995
1341	GUGGGGGA G CGUGUCAG	3710	CTGACACG GGCTAGCTACAACGA TCCCCCAC	4996
1343	GGGGGAGC G UGUCAGAA	3711	TTCTGACA GGCTAGCTACAACGA GCTCCCCC	4997
1345	GGGAGCGU G UCAGAAUC	3712	GATTCTGA GGCTAGCTACAACGA ACGCTCCC	4998
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1357	GAAUCCCU G CGAAGUAC	3714	GTACTTCG GGCTAGCTACAACGA AGGGATTC	5000
1362	CCUGCGAA G UACCUUGG	3715	CCAAGGTA GGCTAGCTACAACGA TTCGCAGG	5001
1364	UGCGAAGU A CCUUGGUU	3716	AACCAAGG GGCTAGCTACAACGA ACTTCGCA	5002
1370	GUACCUUG G UUACCCAC	3717	GTGGGTAA GGCTAGCTACAACGA CAAGGTAC	5003
1373	CCUUGGUU A CCCACCCC	3718	GGGGTGGG GGCTAGCTACAACGA AACCAAGG	5004

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1392	GAAAUAAA A UGGUAUAA	3721	TTATACCA GGCTAGCTACAACGA TTTATTTC	5007
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1410	AAUGGAAU A CCCCUUGA	3726	TCAAGGGG GGCTAGCTACAACGA ATTCCATT	5012
1419	CCCCUUGA G UCCAAUCA	3727	TGATTGGA GGCTAGCTACAACGA TCAAGGGG	5013
1424	UGAGUCCA A UCACACAA	3728	TTGTGTGA GGCTAGCTACAACGA TGGACTCA	5014
1427	GUCCAAUC A CACAAUUA	3729	TAATTGTG GGCTAGCTACAACGA GATTGGAC	5015
1429	CCAAUCAC A CAAUUAAA	3730	TTTAATTG GGCTAGCTACAACGA GTGATTGG	5016
1432	AUCACACA A UUAAAGCG	3731	CGCTTTAA GGCTAGCTACAACGA TGTGTGAT	5017
1438	CAAUUAAA G CGGGGCAU	3732	ATGCCCCG GGCTAGCTACAACGA TTTAATTG	5018
1443	AAAGCGGG G CAUGUACU	3733	AGTACATG GGCTAGCTACAACGA CCCGCTTT	5019
1445	AGCGGGGC A UGUACUGA	3734	TCAGTACA GGCTAGCTACAACGA GCCCCGCT	5020
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1449	GGGCAUGU A CUGACGAU	3736	ATCGTCAG GGCTAGCTACAACGA ACATGCCC	5022
1453	AUGUACUG A CGAUUAUG	3737	CATAATCG GGCTAGCTACAACGA CAGTACAT	5023
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1459	UGACGAUU A UGGAAGUG	3739	CACTTCCA GGCTAGCTACAACGA AATCGTCA	5025
1465	UUAUGGAA G UGAGUGAA	3740	TTCACTCA GGCTAGCTACAACGA TTCCATAA	5026
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1490	AGGAAAUU A CACUGUCA	3745	TGACAGTG GGCTAGCTACAACGA AATTTCCT	5031
1492	GAAAUUAC A CUGUCAUC	3746	GATGACAG GGCTAGCTACAACGA GTAATTTC	5032
1495	AUUACACU G UCAUCCUU	3747	AAGGATGA GGCTAGCTACAACGA AGTGTAAT	5033
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1508	CCUUACCA A UCCCAUUU	3750	AAATGGGA GGCTAGCTACAACGA TGGTAAGG	5036
1513	CCAAUCCC A UUUCAAAG	3751	CTTTGAAA GGCTAGCTACAACGA GGGATTGG	5037
1527	AAGGAGAA G CAGAGCCA	3752	TGGCTCTG GGCTAGCTACAACGA TTCTCCTT	5038
1532	GAAGCAGA G CCAUGUGG	3753	CCACATGG GGCTAGCTACAACGA TCTGCTTC	5039
1535	GCAGAGCC A UGUGGUCU	3754	AGACCACA GGCTAGCTACAACGA GGCTCTGC	5040
1537	AGAGCCAU G UGGUCUCU	3755	AGAGACCA GGCTAGCTACAACGA ATGGCTCT	5041
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1552	CUCUGGUU G UGUAUGUC	3758	GACATACA GGCTAGCTACAACGA AACCAGAG	5044
1554	CUGGUUGU G UAUGUCCC	3759	GGGACATA GGCTAGCTACAACGA ACAACCAG	5045
1556	GGUUGUGU A UGUCCCAC	3760	GTGGGACA GGCTAGCTACAACGA ACACAACC	5046
1558	UUGUGUAU G UCCCACCC	3761	GGGTGGGA GGCTAGCTACAACGA ATACACAA	5047
1563	UAUGUCCC A CCCCAGAU	3762	ATCTGGGG GGCTAGCTACAACGA GGGACATA	5048
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1588	AAUCUCUA A UCUCUCCU	3766	AGGAGAGA GGCTAGCTACAACGA TAGAGATT	5052
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1611	UCCUACCA G UACGGCAC	3770	GTGCCGTA GGCTAGCTACAACGA TGGTAGGA	5056
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1621	ACGGCACC A CUCAAACG	3774	CGTTTGAG GGCTAGCTACAACGA GGTGCCGT	5060
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1646	UACGGUCU A UGCCAUUC	3782	GAATGGCA GGCTAGCTACAACGA AGACCGTA	5068
1648	CGGUCUAU G CCAUUCCU	3783	AGGAATGG GGCTAGCTACAACGA ATAGACCG	5069
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1662	CCUCCCCC G CAUCACAU	3785	ATGTGATG GGCTAGCTACAACGA GGGGGAGG	5071
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1667	CCCGCAUC A CAUCCACU	3787	AGTGGATG GGCTAGCTACAACGA GATGCGGG	5073
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1677	AUCCACUG G UAUUGGCA	3790	TGCCAATA GGCTAGCTACAACGA CAGTGGAT	5076
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1855	GUACCCUU G UUAUCCAA	3825	TTGGATAA GGCTAGCTACAACGA AAGGGTAC	5111
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1963	CUGAAAUU A CUUUGCAA	3848	TTGCAAAG GGCTAGCTACAACGA AATTTCAG	5134
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1978	AACCUGAC A UGCAGCCC	3852	GGGCTGCA GGCTAGCTACAACGA GTCAGGTT	5138
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2017	UGUGGUGC A CUGCAGAC	3863	GTCTGCAG GGCTAGCTACAACGA GCACCACA	5149
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2024	CACUGCAG A CAGAUCUA	3865	TAGATCTG GGCTAGCTACAACGA CTGCAGTG	5151
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2032	ACAGAUCU A CGUUUGAG	3867	CTCAAACG GGCTAGCTACAACGA AGATCTGT	5153
2034	AGAUCUAC G UUUGAGAA	3868	TTCTCAAA GGCTAGCTACAACGA GTAGATCT	5154
2042	GUUUGAGA A CCUCACAU	3869	ATGTGAGG GGCTAGCTACAACGA TCTCAAAC	5155
2047	AGAACCUC A CAUGGUAC	3870	GTACCATG GGCTAGCTACAACGA GAGGTTCT	5156
2049	AACCUCAC A UGGUACAA	3871	TTGTACCA GGCTAGCTACAACGA GTGAGGTT	5157
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2054	CACAUGGU A CAAGCUUG	3873	CAAGCTTG GGCTAGCTACAACGA ACCATGTG	5159
2058	UGGUACAA G CUUGGCCC	3874	GGGCCAAG GGCTAGCTACAACGA TTGTACCA	5160
2063	CAAGCUUG G CCCACAGC	3875	GCTGTGGG GGCTAGCTACAACGA CAAGCTTG	5161
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2141	GAAAUUGA A UGCCACCA	3892	TGGTGGCA GGCTAGCTACAACGA TCAATTTC	5178
2143	AAUUGAAU G CCACCAUG	3893	CATGGTGG GGCTAGCTACAACGA ATTCAATT	5179
2146	UGAAUGCC A CCAUGUUC	3894	GAACATGG GGCTAGCTACAACGA GGCATTCA	5180
2149	AUGCCACC A UGUUCUCU	3895	AGAGAACA GGCTAGCTACAACGA GGTGGCAT	5181
2151	GCCACCAU G UUCUCUAA	3896	TTAGAGAA GGCTAGCTACAACGA ATGGTGGC	5182
2159	GUUCUCUA A UAGCACAA	3897	TTGTGCTA GGCTAGCTACAACGA TAGAGAAC	5183
2162	CUCUAAUA G CACAAAUG	3898	CATTTGTG GGCTAGCTACAACGA TATTAGAG	5184
2164	CUAAUAGC A CAAAUGAC	3899	GTCATTTG GGCTAGCTACAACGA GCTATTAG	5185
2168	UAGCACAA A UGACAUUU	3900	AAATGTCA GGCTAGCTACAACGA TTGTGCTA	5186
2171	CACAAAUG A CAUUUUGA	3901	TCAAAATG GGCTAGCTACAACGA CATTTGTG	5187
2173	CAAAUGAC A UUUUGAUC	3902	GATCAAAA GGCTAGCTACAACGA GTCATTTG	5188
2179	ACAUUUUG A UCAUGGAG	3903	CTCCATGA GGCTAGCTACAACGA CAAAATGT	5189
2182	UUUUGAUC A UGGAGCUU	3904	AAGCTCCA GGCTAGCTACAACGA GATCAAAA	5190
2187	AUCAUGGA G CUUAAGAA	3905	TTCTTAAG GGCTAGCTACAACGA TCCATGAT	5191
2195	GCUUAAGA A UGCAUCCU	3906	AGGATGCA GGCTAGCTACAACGA TCTTAAGC	5192
2197	UUAAGAAU G CAUCCUUG	3907	CAAGGATG GGCTAGCTACAACGA ATTCTTAA	5193
2199	AAGAAUGC A UCCUUGCA	3908	TGCAAGGA GGCTAGCTACAACGA GCATTCTT	5194
2205	GCAUCCUU G CAGGACCA	3909	TGGTCCTG GGCTAGCTACAACGA AAGGATGC	5195
2210	CUUGCAGG A CCAAGGAG	3910	CTCCTTGG GGCTAGCTACAACGA CCTGCAAG	5196
2219	CCAAGGAG A CUAUGUCU	3911	AGACATAG GGCTAGCTACAACGA CTCCTTGG	5197
2222	AGGAGACU A UGUCUGCC	3912	GGCAGACA GGCTAGCTACAACGA AGTCTCCT	5198
2224	GAGACUAU G UCUGCCUU	3913	AAGGCAGA GGCTAGCTACAACGA ATAGTCTC	5199
2228	CUAUGUCU G CCUUGCUC	3914	GAGCAAGG GGCTAGCTACAACGA AGACATAG	5200
2233	UCUGCCUU G CUCAAGAC	3915	GTCTTGAG GGCTAGCTACAACGA AAGGCAGA	5201
2240	UGCUCAAG A CAGGAAGA	3916	TCTTCCTG GGCTAGCTACAACGA CTTGAGCA	5202
2248	ACAGGAAG A CCAAGAAA	3917	TTTCTTGG GGCTAGCTACAACGA CTTCCTGT	5203
2259	AAGAAAAG A CAUUGCGU	3918	ACGCAATG GGCTAGCTACAACGA CTTTTCTT	5204
2261	GAAAAGAC A UUGCGUGG	3919	CCACGCAA GGCTAGCTACAACGA GTCTTTTC	5205
2264	AAGACAUU G CGUGGUCA	3920	TGACCACG GGCTAGCTACAACGA AATGTCTT	5206
2266	GACAUUGC G UGGUCAGG	3921	CCTGACCA GGCTAGCTACAACGA GCAATGTC	5207
2269	AUUGCGUG G UCAGGCAG	3922	CTGCCTGA GGCTAGCTACAACGA CACGCAAT	5208
2274	GUGGUCAG G CAGCUCAC	3923	GTGAGCTG GGCTAGCTACAACGA CTGACCAC	5209
2277	GUCAGGCA G CUCACAGU	3924	ACTGTGAG GGCTAGCTACAACGA TGCCTGAC	5210
2281	GGCAGCUC A CAGUCCUA	3925	TAGGACTG GGCTAGCTACAACGA GAGCTGCC	5211
2284	AGCUCACA G UCCUAGAG	3926	CTCTAGGA GGCTAGCTACAACGA TGTGAGCT	5212
2292	GUCCUAGA G CGUGUGGC	3927	GCCACACG GGCTAGCTACAACGA TCTAGGAC	5213
2294	CCUAGAGC G UGUGGCAC	3928	GTGCCACA GGCTAGCTACAACGA GCTCTAGG	5214
2296	UAGAGCGU G UGGCACCC	3929	GGGTGCCA GGCTAGCTACAACGA ACGCTCTA	5215
2299	AGCGUGUG G CACCCACG	3930	CGTGGGTG GGCTAGCTACAACGA CACACGCT	5216

2301	CGUGUGGC A CCCACGAU	3931	ATCGTGGG GGCTAGCTACAACGA GCCACACG	5217
2305	UGGCACCC A CGAUCACA	3932	TGTGATCG GGCTAGCTACAACGA GGGTGCCA	5218
2308	CACCCACG A UCACAGGA	3933	TCCTGTGA GGCTAGCTACAACGA CGTGGGTG	5219
2311	CCACGAUC A CAGGAAAC	3934	GTTTCCTG GGCTAGCTACAACGA GATCGTGG	5220
2318	CACAGGAA A CCUGGAGA	3935	TCTCCAGG GGCTAGCTACAACGA TTCCTGTG	5221
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2339	GACGACAA G UAUUGGGG	3939	CCCCAATA GGCTAGCTACAACGA TTGTCGTC	5225
2341	CGACAAGU A UUGGGGAA	3940	TTCCCCAA GGCTAGCTACAACGA ACTTGTCG	5226
2351	UGGGGAAA G CAUCGAAG	3941	CTTCGATG GGCTAGCTACAACGA TTTCCCCA	5227
2353	GGGAAAGC A UCGAAGUC	3942	GACTTCGA GGCTAGCTACAACGA GCTTTCCC	5228
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2373	UGCACGGC A UCUGGGAA	3948	TTCCCAGA GGCTAGCTACAACGA GCCGTGCA	5234
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2391	CCCCCUCC A CAGAUCAU	3950	ATGATCTG GGCTAGCTACAACGA GGAGGGGG	5236
2395	CUCCACAG A UCAUGUGG	3951	CCACATGA GGCTAGCTACAACGA CTGTGGAG	5237
2398	CACAGAUC A UGUGGUUU	3952	AAACCACA GGCTAGCTACAACGA GATCTGTG	5238
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2414	UAAAGAUA A UGAGACCC	3956	GGGTCTCA GGCTAGCTACAACGA TATCTTTA	5242
2419	AUAAUGAG A CCCUUGUA	3957	TACAAGGG GGCTAGCTACAACGA CTCATTAT	5243
2425	AGACCCUU G UAGAAGAC	3958	GTCTTCTA GGCTAGCTACAACGA AAGGGTCT	5244
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2438	AGACUCAG G CAUUGUAU	3960	ATACAATG GGCTAGCTACAACGA CTGAGTCT	5246
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2443	CAGGCAUU G UAUUGAAG	3962	CTTCAATA GGCTAGCTACAACGA AATGCCTG	5248
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2465	GAACCGGA A CCUCACUA	3966	TAGTGAGG GGCTAGCTACAACGA TCCGGTTC	5252
2470	GGAACCUC A CUAUCCGC	3967	GCGGATAG GGCTAGCTACAACGA GAGGTTCC	5253
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2477	CACUAUCC G CAGAGUGA	3969	TCACTCTG GGCTAGCTACAACGA GGATAGTG	5255
2482	UCCGCAGA G UGAGGAAG	3970	CTTCCTCA GGCTAGCTACAACGA TCTGCGGA	5256
2495	GAAGGAGG A CGAAGGCC	3971	GGCCTTCG GGCTAGCTACAACGA CCTCCTTC	5257
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2507	AGGCCUCU A CACCUGCC	3973	GGCAGGTG GGCTAGCTACAACGA AGAGGCCT	5259
2509	GCCUCUAC A CCUGCCAG	3974	CTGGCAGG GGCTAGCTACAACGA GTAGAGGC	5260
2513	CUACACCU G CCAGGCAU	3975	ATGCCTGG GGCTAGCTACAACGA AGGTGTAG	5261
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2520	UGCCAGGC A UGCAGUGU	3977	ACACTGCA GGCTAGCTACAACGA GCCTGGCA	5263
2522	CCAGGCAU G CAGUGUUC	3978	GAACACTG GGCTAGCTACAACGA ATGCCTGG	5264
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2527	CAUGCAGU G UUCUUGGC	3980	GCCAAGAA GGCTAGCTACAACGA ACTGCATG	5266
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2537	UCUUGGCU G UGCAAAAG	3982	CTTTTGCA GGCTAGCTACAACGA AGCCAAGA	5268
2539	UUGGCUGU G CAAAAGUG	3983	CACTTTTG GGCTAGCTACAACGA ACAGCCAA	5269

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2553	GUGGAGGC A UUUUUCAU	3986	ATGAAAAA GGCTAGCTACAACGA GCCTCCAC	5272
2560	CAUUUUUC A UAAUAGAA	3987	TTCTATTA GGCTAGCTACAACGA GAAAAATG	5273
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2570	AAUAGAAG G UGCCCAGG	3989	CCTGGGCA GGCTAGCTACAACGA CTTCTATT	5275
2572	UAGAAGGU G CCCAGGAA	3990	TTCCTGGG GGCTAGCTACAACGA ACCTTCTA	5276
2584	AGGAAAAG A CGAACUUG	3991	CAAGTTCG GGCTAGCTACAACGA CTTTTCCT	5277
2588	AAAGACGA A CUUGGAAA	3992	TTTCCAAG GGCTAGCTACAACGA TCGTCTTT	5278
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2626	CGGUGAUU G CCAUGUUC	4002	GAACATGG GGCTAGCTACAACGA AATCACCG	5288
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2631	AUUGCCAU G UUCUUCUG	4004	CAGAAGAA GGCTAGCTACAACGA ATGGCAAT	5290
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2656	UUGUCAUC A UCCUACGG	4009	CCGTAGGA GGCTAGCTACAACGA GATGACAA	5295
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2698	AACUGAAG A CAGGCUAC	4017	GTAGCCTG GGCTAGCTACAACGA CTTCAGTT	5303
2702	GAAGACAG G CUACUUGU	4018	ACAAGTAG GGCTAGCTACAACGA CTGTCTTC	5304
2705	GACAGGCU A CUUGUCCA	4019	TGGACAAG GGCTAGCTACAACGA AGCCTGTC	5305
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2713	ACUUGUCC A UCGUCAUG	4021	CATGACGA GGCTAGCTACAACGA GGACAAGT	5307
2716	UGUCCAUC G UCAUGGAU	4022	ATCCATGA GGCTAGCTACAACGA GATGGACA	5308
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2723	CGUCAUGG A UCCAGAUG	4024	CATCTGGA GGCTAGCTACAACGA CCATGACG	5310
2729	GGAUCCAG A UGAACUCC	4025	GGAGTTCA GGCTAGCTACAACGA CTGGATCC	5311
2733	CCAGAUGA A CUCCCAUU	4026	AATGGGAG GGCTAGCTACAACGA TCATCTGG	5312
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2753	UGAACAUU G UGAACGAC	4031	GTCGTTCA GGCTAGCTACAACGA AATGTTCA	5317
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2760	UGUGAACG A CUGCCUUA	4033	TAAGGCAG GGCTAGCTACAACGA CGTTCACA	5319
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2768	ACUGCCUU A UGAUGCCA	4035	TGGCATCA GGCTAGCTACAACGA AAGGCAGT	5321
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2773	CUUAUGAU G CCAGCAAA	4037	TTTGCTGG GGCTAGCTACAACGA ATCATAAG	5323
2777	UGAUGCCA G CAAAUGGG	4038	CCCATTTG GGCTAGCTACAACGA TGGCATCA	5324
2781	GCCAGCAA A UGGGAAUU	4039	AATTCCCA GGCTAGCTACAACGA TTGCTGGC	5325
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2825	GCCUCUUG G CCGUGGUG	4046	CACCACGG GGCTAGCTACAACGA CAAGAGGC	5332
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2831	UGGCCGUG G UGCCUUUG	4048	CAAAGGCA GGCTAGCTACAACGA CACGGCCA	5334
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2896	GCAGGACA G UAGCAGUC	4063	GACTGCTA GGCTAGCTACAACGA TGTCCTGC	5349
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2971	AGAUCCUC A UUCAUAUU	4080	AATATGAA GGCTAGCTACAACGA GAGGATCT	5366
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3116	UGUCCCCU A CAAGACCA	4112	TGGTCTTG GGCTAGCTACAACGA AGGGGACA	5398
3121	CCUACAAG A CCAAAGGG	4113	CCCTTTGG GGCTAGCTACAACGA CTTGTAGG	5399
3130	CCAAAGGG G CACGAUUC	4114	GAATCGTG GGCTAGCTACAACGA CCCTTTGG	5400
3132	AAAGGGGC A CGAUUCCG	4115	CGGAATCG GGCTAGCTACAACGA GCCCCTTT	5401
3135	GGGGCACG A UUCCGUCA	4116	TGACGGAA GGCTAGCTACAACGA CGTGCCCC	5402
3140	ACGAUUCC G UCAAGGGA	4117	TCCCTTGA GGCTAGCTACAACGA GGAATCGT	5403
3152	AGGGAAAG A CUACGUUG	4118	CAACGTAG GGCTAGCTACAACGA CTTTCCCT	5404
3155	GAAAGACU A CGUUGGAG	4119	CTCCAACG GGCTAGCTACAACGA AGTCTTTC	5405
3157	AAGACUAC G UUGGAGCA	4120	TGCTCCAA GGCTAGCTACAACGA GTAGTCTT	5406
3163	ACGUUGGA G CAAUCCCU	4121	AGGGATTG GGCTAGCTACAACGA TCCAACGT	5407
3166	UUGGAGCA A UCCCUGUG	4122	CACAGGGA GGCTAGCTACAACGA TGCTCCAA	5408
3172	CAAUCCCU G UGGAUCUG	4123	CAGATCCA GGCTAGCTACAACGA AGGGATTG	5409
3176	CCCUGUGG A UCUGAAAC	4124	GTTTCAGA GGCTAGCTACAACGA CCACAGGG	5410
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3186	CUGAAACG G CGCUUGGA	4126	TCCAAGCG GGCTAGCTACAACGA CGTTTCAG	5412
3188	GAAACGGC G CUUGGACA	4127	TGTCCAAG GGCTAGCTACAACGA GCCGTTTC	5413
3194	GCGCUUGG A CAGCAUCA	4128	TGATGCTG GGCTAGCTACAACGA CCAAGCGC	5414
3197	CUUGGACA G CAUCACCA	4129	TGGTGATG GGCTAGCTACAACGA TGTCCAAG	5415
3199	UGGACAGC A UCACCAGU	4130	ACTGGTGA GGCTAGCTACAACGA GCTGTCCA	5416
3202	ACAGCAUC A CCAGUAGC	4131	GCTACTGG GGCTAGCTACAACGA GATGCTGT	5417
3206	CAUCACCA G UAGCCAGA	4132	TCTGGCTA GGCTAGCTACAACGA TGGTGATG	5418
3209	CACCAGUA G CCAGAGCU	4133	AGCTCTGG GGCTAGCTACAACGA TACTGGTG	5419
3215	UAGCCAGA G CUCAGCCA	4134	TGGCTGAG GGCTAGCTACAACGA TCTGGCTA	5420
3220	AGAGCUCA G CCAGCUCU	4135	AGAGCTGG GGCTAGCTACAACGA TGAGCTCT	5421
3224	CUCAGCCA G CUCUGGAU	4136	ATCCAGAG GGCTAGCTACAACGA TGGCTGAG	5422
3231	AGCUCUGG A UUUGUGGA	4137	TCCACAAA GGCTAGCTACAACGA CCAGAGCT	5423
3235	CUGGAUUU G UGGAGGAG	4138	CTCCTCCA GGCTAGCTACAACGA AAATCCAG	5424
3246	GAGGAGAA G UCCCUCAG	4139	CTGAGGGA GGCTAGCTACAACGA TTCTCCTC	5425
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3257	CCUCAGUG A UGUAGAAG	4141	CTTCTACA GGCTAGCTACAACGA CACTGAGG	5427
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3288	GAAGAUCU G UAUAAGGA	4145	TCCTTATA GGCTAGCTACAACGA AGATCTTC	5431
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3319	AGCAUCUC A UCUGUUAC	4151	GTAACAGA GGCTAGCTACAACGA GAGATGCT	5437
3323	UCUCAUCU G UUACAGCU	4152	AGCTGTAA GGCTAGCTACAACGA AGATGAGA	5438
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3329	CUGUUACA G CUUCCAAG	4154	CTTGGAAG GGCTAGCTACAACGA TGTAACAG	5440
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3354	GGCAUGGA G UUCUUGGC	4159	GCCAAGAA GGCTAGCTACAACGA TCCATGCC	5445
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3372	UCGCGAAA G UGUAUCCA	4163	TGGATACA GGCTAGCTACAACGA TTTCGCGA	5449
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3394	ACCUGGCG G CACGAAAU	4169	ATTTCGTG GGCTAGCTACAACGA CGCCAGGT	5455
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3411	AUCCUCUU A UCGGAGAA	4173	TTCTCCGA GGCTAGCTACAACGA AAGAGGAT	5459
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3481	CAGAUUAU G UCAGAAAA	4188	TTTTCTGA GGCTAGCTACAACGA ATAATCTG	5474
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3496	AAGGAGAU G CUCGCCUC	4190	GAGGCGAG GGCTAGCTACAACGA ATCTCCTT	5476
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3517	UGAAAUGG A UGGCCCCA	4193	TGGGGCCA GGCTAGCTACAACGA CCATTTCA	5479
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4186	AGUCUGUG G CAUCUGAA	4334	TTCAGATG GGCTAGCTACAACGA CACAGACT	5620
4188	UCUGUGGC A UCUGAAGG	4335	CCTTCAGA GGCTAGCTACAACGA GCCACAGA	5621
4196	AUCUGAAG G CUCAAACC	4336	GGTTTGAG GGCTAGCTACAACGA CTTCAGAT	5622
4202	AGGCUCAA A CCAGACAA	4337	TTGTCTGG GGCTAGCTACAACGA TTGAGCCT	5623
4207	CAAACCAG A CAAGCGGC	4338	GCCGCTTG GGCTAGCTACAACGA CTGGTTTG	5624
4211	CCAGACAA G CGGCUACC	4339	GGTAGCCG GGCTAGCTACAACGA TTGTCTGG	5625
4214	GACAAGCG G CUACCAGU	4340	ACTGGTAG GGCTAGCTACAACGA CGCTTGTC	5626
4217	AAGCGGCU A CCAGUCCG	4341	CGGACTGG GGCTAGCTACAACGA AGCCGCTT	5627
4221	GGCUACCA G UCCGGAUA	4342	TATCCGGA GGCTAGCTACAACGA TGGTAGCC	5628
4227	CAGUCCGG A UAUCACUC	4343	GAGTGATA GGCTAGCTACAACGA CCGGACTG	5629
4229	GUCCGGAU A UCACUCCG	4344	CGGAGTGA GGCTAGCTACAACGA ATCCGGAC	5630
4232	CGGAUAUC A CUCCGAUG	4345	CATCGGAG GGCTAGCTACAACGA GATATCCG	5631
4238	UCACUCCG A UGACACAG	4346	CTGTGTCA GGCTAGCTACAACGA CGGAGTGA	5632
4241	CUCCGAUG A CACAGACA	4347	TGTCTGTG GGCTAGCTACAACGA CATCGGAG	5633
4243	CCGAUGAC A CAGACACC	4348	GGTGTCTG GGCTAGCTACAACGA GTCATCGG	5634
4247	UGACACAG A CACCACCG	4349	CGGTGGTG GGCTAGCTACAACGA CTGTGTCA	5635
4249	ACACAGAC A CCACCGUG	4350	CACGGTGG GGCTAGCTACAACGA GTCTGTGT	5636
4252	CAGACACC A CCGUGUAC	4351	GTACACGG GGCTAGCTACAACGA GGTGTCTG	5637
4255	ACACCACC G UGUACUCC	4352	GGAGTACA GGCTAGCTACAACGA GGTGGTGT	5638
4257	ACCACCGU G UACUCCAG	4353	CTGGAGTA GGCTAGCTACAACGA ACGGTGGT	5639.
4259	CACCGUGU A CUCCAGUG	4354	CACTGGAG GGCTAGCTACAACGA ACACGGTG	5640

4265	GUACUCCA G UGAGGAAG	4355	CTTCCTCA GGCTAGCTACAACGA TGGAGTAC	5641
4273	GUGAGGAA G CAGAACUU	4356	AAGTTCTG GGCTAGCTACAACGA TTCCTCAC	5642
4278	GAAGCAGA A CUUUUAAA	4357	TTTAAAAG GGCTAGCTACAACGA TCTGCTTC	5643
4287	CUUUUAAA G CUGAUAGA	4358	TCTATCAG GGCTAGCTACAACGA TTTAAAAG	5644
4291	UAAAGCUG A UAGAGAUU	4359	AATCTCTA GGCTAGCTACAACGA CAGCTTTA	5645
4297	UGAUAGAG A UUGGAGUG	4360	CACTCCAA GGCTAGCTACAACGA CTCTATCA	5646
4303	AGAUUGGA G UGCAAACC	4361	GGTTTGCA GGCTAGCTACAACGA TCCAATCT	5647
4305	AUUGGAGU G CAAACCGG	4362	CCGGTTTG GGCTAGCTACAACGA ACTCCAAT	5648
4309	GAGUGCAA A CCGGUAGC	4363	GCTACCGG GGCTAGCTACAACGA TTGCACTC	5649
4313	GCAAACCG G UAGCACAG	4364	CTGTGCTA GGCTAGCTACAACGA CGGTTTGC	5650
4316	AACCGGUA G CACAGCCC	4365	GGGCTGTG GGCTAGCTACAACGA TACCGGTT	5651
4318	CCGGUAGC A CAGCCCAG	4366	CTGGGCTG GGCTAGCTACAACGA GCTACCGG	5652
4321	GUAGCACA G CCCAGAUU	4367	AATCTGGG GGCTAGCTACAACGA TGTGCTAC	5653
4327	CAGCCCAG A UUCUCCAG	4368	CTGGAGAA GGCTAGCTACAACGA CTGGGCTG	5654
4335	AUUCUCCA G CCUGACUC	4369	GAGTCAGG GGCTAGCTACAACGA TGGAGAAT	5655
4340	CCAGCCUG A CUCGGGGA	4370	TCCCCGAG GGCTAGCTACAACGA CAGGCTGG	5656
4348	ACUCGGGG A CCACACUG	4371	CAGTGTGG GGCTAGCTACAACGA CCCCGAGT	5657
4351	CGGGGACC A CACUGAGC	4372	GCTCAGTG GGCTAGCTACAACGA GGTCCCCG	5658
4353	GGGACCAC A CUGAGCUC	4373	GAGCTCAG GGCTAGCTACAACGA GTGGTCCC	5659
4358	CACACUGA G CUCUCCUC	4374	GAGGAGAG GGCTAGCTACAACGA TCAGTGTG	5660
4369	CUCCUCCU G UUUAAAAG	4375	CTTTTAAA GGCTAGCTACAACGA AGGAGGAG	5661
4381	AAAAGGAA G CAUCCACA	4376	TGTGGATG GGCTAGCTACAACGA TTCCTTTT	5662
4383	AAGGAAGC A UCCACACC	4377	GGTGTGGA GGCTAGCTACAACGA GCTTCCTT	5663
4387	AAGCAUCC A CACCCCAA	4378	TTGGGGTG GGCTAGCTACAACGA GGATGCTT	5664
4389	GCAUCCAC A CCCCAACU	4379	AGTTGGGG GGCTAGCTACAACGA GTGGATGC	5665
4395	ACACCCCA A CUCCCGGA	4380	TCCGGGAG GGCTAGCTACAACGA TGGGGTGT	5666
4403	ACUCCCGG A CAUCACAU	4381	ATGTGATG GGCTAGCTACAACGA CCGGGAGT	5667
4405	UCCCGGAC A UCACAUGA	4382	TCATGTGA GGCTAGCTACAACGA GTCCGGGA	5668
4408	CGGACAUC A CAUGAGAG	4383	CTCTCATG GGCTAGCTACAACGA GATGTCCG	5669
4410	GACAUCAC A UGAGAGGU	4384	ACCTCTCA GGCTAGCTACAACGA GTGATGTC	5670
4417	CAUGAGAG G UCUGCUCA	4385	TGAGCAGA GGCTAGCTACAACGA CTCTCATG	5671
4421	AGAGGUCU G CUCAGAUU	4386	AATCTGAG GGCTAGCTACAACGA AGACCTCT	5672
4427	CUGCUCAG A UUUUGAAG	4387	CTTCAAAA GGCTAGCTACAACGA CTGAGCAG	5673
4435	AUUUUGAA G UGUUGUUC	4388	GAACAACA GGCTAGCTACAACGA TTCAAAAT	5674
4437	UUUGAAGU G UUGUUCUU	4389	AAGAACAA GGCTAGCTACAACGA ACTTCAAA	5675
4440	GAAGUGUU G UUCUUUCC	4390	GGAAAGAA GGCTAGCTACAACGA AACACTTC	5676
4449	UUCUUUCC A CCAGCAGG	4391	CCTGCTGG GGCTAGCTACAACGA GGAAAGAA	5677
4453	UUCCACCA G CAGGAAGU	4392	ACTTCCTG GGCTAGCTACAACGA TGGTGGAA	5678
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4463	AGGAAGUA G CCGCAUUU	4394	AAATGCGG GGCTAGCTACAACGA TACTTCCT	5680
4466	AAGUAGCC G CAUUUGAU	4395	ATCAAATG GGCTAGCTACAACGA GGCTACTT	5681
4468	GUAGCCGC A UUUGAUUU	4396	AAATCAAA GGCTAGCTACAACGA GCGGCTAC	5682
4473	CGCAUUUG A UUUUCAUU	4397	AATGAAAA GGCTAGCTACAACGA CAAATGCG	5683
4479	UGAUUUUC A UUUCGACA	4398	TGTCGAAA GGCTAGCTACAACGA GAAAATCA	5684
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4488	UUUCGACA A CAGAAAAA	4400	TTTTTCTG GGCTAGCTACAACGA TGTCGAAA	5686
4499	GAAAAAGG A CCUCGGAC	4401	GTCCGAGG GGCTAGCTACAACGA CCTTTTTC	5687
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4509	CUCGGACU G CAGGGAGC	4403	GCTCCCTG GGCTAGCTACAACGA AGTCCGAG	5689
4516	UGCAGGGA G CCAGUCUU	4404	AAGACTGG GGCTAGCTACAACGA TCCCTGCA	5690
4520	GGGAGCCA G UCUUCUAG	4405	CTAGAAGA GGCTAGCTACAACGA TGGCTCCC	5691
4529	UCUUCUAG G CAUAUCCU	4406	AGGATATG GGCTAGCTACAACGA CTAGAAGA	5692
4531	UUCUAGGC A UAUCCUGG	4407	CCAGGATA GGCTAGCTACAACGA GCCTAGAA	5693

4533	CUAGGCAU A UCCUGGAA	4408	TTCCAGGA GGCTAGCTACAACGA ATGCCTAG	5694
4545	UGGAAGAG G CUUGUGAC	4409	GTCACAAG GGCTAGCTACAACGA CTCTTCCA	5695
4549	AGAGGCUU G UGACCCAA	4410	TTGGGTCA GGCTAGCTACAACGA AAGCCTCT	5696
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4560	ACCCAAGA A UGUGUCUG	4412	CAGACACA GGCTAGCTACAACGA TCTTGGGT	5698
4562	CCAAGAAU G UGUCUGUG	4413	CACAGACA GGCTAGCTACAACGA ATTCTTGG	5699
4564	AAGAAUGU G UCUGUGUC	4414	GACACAGA GGCTAGCTACAACGA ACATTCTT	5700
4568	AUGUGUCU G UGUCUUCU	4415	AGAAGACA GGCTAGCTACAACGA AGACACAT	5701
4570	GUGUCUGU G UCUUCUCC	4416	GGAGAAGA GGCTAGCTACAACGA ACAGACAC	5702
4581	UUCUCCCA G UGUUGACC	4417	GGTCAACA GGCTAGCTACAACGA TGGGAGAA	5703
4583	CUCCCAGU G UUGACCUG	4418	CAGGTCAA GGCTAGCTACAACGA ACTGGGAG	5704
4587	CAGUGUUG A CCUGAUCC	4419	GGATCAGG GGCTAGCTACAACGA CAACACTG	5705
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4618	UUUAAAAA G CAUUAUCA	4423	TGATAATG GGCTAGCTACAACGA TTTTTAAA	5709
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4623	AAAGCAUU A UCAUGCCC	4425	GGGCATGA GGCTAGCTACAACGA AATGCTTT	5711
4626	GCAUUAUC A UGCCCCUG	4426	CAGGGGCA GGCTAGCTACAACGA GATAATGC	5712
4628	AUUAUCAU G CCCCUGCU	4427	AGCAGGGG GGCTAGCTACAACGA ATGATAAT	5713
4634	AUGCCCCU G CUGCGGGU	4428	ACCCGCAG GGCTAGCTACAACGA AGGGGCAT	5714
4637	CCCCUGCU G CGGGUCUC	4429	GAGACCCG GGCTAGCTACAACGA AGCAGGGG	5715
4641	UGCUGCGG G UCUCACCA	4430	TGGTGAGA GGCTAGCTACAACGA CCGCAGCA	5716
4646	CGGGUCUC A CCAUGGGU	4431	ACCCATGG GGCTAGCTACAACGA GAGACCCG	5717
4649	GUCUCACC A UGGGUUUA	4432	TAAACCCA GGCTAGCTACAACGA GGTGAGAC	5718
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4660	GGUUUAGA A CAAAGAGC	4434	GCTCTTTG GGCTAGCTACAACGA TCTAAACC	5720
4667	AACAAAGA G CUUCAAGC	4435	GCTTGAAG GGCTAGCTACAACGA TCTTTGTT	5721
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4677	UUCAAGCA A UGGCCCCA	4437	TGGGGCCA GGCTAGCTACAACGA TGCTTGAA	5723
4680	AAGCAAUG G CCCCAUCC	4438	GGATGGGG GGCTAGCTACAACGA CATTGCTT	5724
4685	AUGGCCCC A UCCUCAAA	4439	TTTGAGGA GGCTAGCTACAACGA GGGGCCAT	5725
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4718	GGGAGCUG A CACUUCUG	4445	CAGAAGTG GGCTAGCTACAACGA CAGCTCCC	5731
4720	GAGCUGAC A CUUCUGUA	4446	TACAGAAG GGCTAGCTACAACGA GTCAGCTC	5732
4726	ACACUUCU G UAAAACUA	4447	TAGTTTTA GGCTAGCTACAACGA AGAAGTGT	5733
4731	UCUGUAAA A CUAGAAGA	4448	TCTTCTAG GGCTAGCTACAACGA TTTACAGA	5734
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4751	ACCAGGCA A CGUAAGUG	4452	CACTTACG GGCTAGCTACAACGA TGCCTGGT	5738
4753	CAGGCAAC G UAAGUGUU	4453	AACACTTA GGCTAGCTACAACGA GTTGCCTG	5739
4757	CAACGUAA G UGUUCGAG	4454	CTCGAACA GGCTAGCTACAACGA TTACGTTG	5740
4759	ACGUAAGU G UUCGAGGU	4455	ACCTCGAA GGCTAGCTACAACGA ACTTACGT	5741
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4811	UCCAAGAG G CUUUGUUU	4464	AAACAAAG GGCTAGCTACAACGA CTCTTGGA	5750
4816	GAGGCUUU G UUUAGGAC	4465	GTCCTAAA GGCTAGCTACAACGA AAAGCCTC	5751
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4841	CAAGCCAA G CCUUAAGU	4470	ACTTAAGG GGCTAGCTACAACGA TTGGCTTG	5756
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4850	CCUUAAGU G UGGAAUUC	4472	GAATTCCA GGCTAGCTACAACGA ACTTAAGG	5758
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4881	GAAGACUA A CGUUACCU	4477	AGGTAACG GGCTAGCTACAACGA TAGTCTTC	5763
4883	AGACUAAC G UUACCUUG	4478	CAAGGTAA GGCTAGCTACAACGA GTTAGTCT	5764
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5135	GGCUCCUU G UCUCCCAG	4529	CTGGGAGA GGCTAGCTACAACGA AAGGAGCC	5815
5144	UCUCCCAG G CUGAUCCU	4530	AGGATCAG GGCTAGCTACAACGA CTGGGAGA	5816
5148	CCAGGCUG A UCCUUUAU	4531	ATAAAGGA GGCTAGCTACAACGA CAGCCTGG	5817
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5164	UUCAGAAU A CCACAAAG	4534	CTTTGTGG GGCTAGCTACAACGA ATTCTGAA	5820
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5180	GAAAGGAC A UUCAGCUC	4537	GAGCTGAA GGCTAGCTACAACGA GTCCTTTC	5823
5185	GACAUUCA G CUCAAGGC	4538	GCCTTGAG GGCTAGCTACAACGA TGAATGTC	5824
5192	AGCUCAAG G CUCCCUGC	4539	GCAGGGAG GGCTAGCTACAACGA CTTGAGCT	5825
5199	GGCUCCCU G CCGUGUUG	4540	CAACACGG GGCTAGCTACAACGA AGGGAGCC	5826
5202	UCCCUGCC G UGUUGAAG	4541	CTTCAACA GGCTAGCTACAACGA GGCAGGGA	5827
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5262	AUACCCUC A UAUCUGUC	4553	GACAGATA GGCTAGCTACAACGA GAGGGTAT	5839
5264	ACCCUCAU A UCUGUCCU	4554	AGGACAGA GGCTAGCTACAACGA ATGAGGGT	5840
5268	UCAUAUCU G UCCUGAUG	4555	CATCAGGA GGCTAGCTACAACGA AGATATGA	5841
5274	CUGUCCUG A UGUGAUAU	4556	ATATCACA GGCTAGCTACAACGA CAGGACAG	5842
5276	GUCCUGAU G UGAUAUGU	4557	ACATATCA GGCTAGCTACAACGA ATCAGGAC	5843
5279	CUGAUGUG A UAUGUCUG	4558	CAGACATA GGCTAGCTACAACGA CACATCAG	5844
5281	GAUGUGAU A UGUCUGAG	4559	CTCAGACA GGCTAGCTACAACGA ATCACATC	5845
5283	UGUGAUAU G UCUGAGAC	4560	GTCTCAGA GGCTAGCTACAACGA ATATCACA	5846
5290	UGUCUGAG A CUGAAUGC	4561	GCATTCAG GGCTAGCTACAACGA CTCAGACA	5847
5295	GAGACUGA A UGCGGGAG	4562	CTCCCGCA GGCTAGCTACAACGA TCAGTCTC	5848
5297	GACUGAAU G CGGGAGGU	4563	ACCTCCCG GGCTAGCTACAACGA ATTCAGTC	5849
5304	UGCGGGAG G UUCAAUGU	4564	ACATTGAA GGCTAGCTACAACGA CTCCCGCA	5850
5309	GAGGUUCA A UGUGAAGC	4565	GCTTCACA GGCTAGCTACAACGA TGAACCTC	5851
5311	GGUUCAAU G UGAAGCUG	4566	CAGCTTCA GGCTAGCTACAACGA ATTGAACC	5852

5316	AAUGUGAA G CUGUGUGU	4567	ACACACAG GGCTAGCTACAACGA TTCACATT	5853
5319	GUGAAGCU G UGUGUGGU	4568	ACCACACA GGCTAGCTACAACGA AGCTTCAC	5854
5321	GAAGCUGU G UGUGGUGU	4569	ACACCACA GGCTAGCTACAACGA ACAGCTTC	5855
5323	AGCUGUGU G UGGUGUCA	4570	TGACACCA GGCTAGCTACAACGA ACACAGCT	5856
5326	UGUGUGUG G UGUCAAAG	4571	CTTTGACA GGCTAGCTACAACGA CACACACA	5857
5328	UGUGUGGU G UCAAAGUU	4572	AACTTTGA GGCTAGCTACAACGA ACCACACA	5858
5334	GUGUCAAA G UUUCAGGA	4573	TCCTGAAA GGCTAGCTACAACGA TTTGACAC	5859
5346	CAGGAAGG A UUUUACCC	4574	GGGTAAAA GGCTAGCTACAACGA CCTTCCTG	5860
5351	AGGAUUUU A CCCUUUUG	4575	CAAAAGGG GGCTAGCTACAACGA AAAATCCT	5861
5359	ACCCUUUU G UUCUUCCC	4576	GGGAAGAA GGCTAGCTACAACGA AAAAGGGT	5862
5371	UUCCCCCU G UCCCCAAC	4577	GTTGGGGA GGCTAGCTACAACGA AGGGGGAA	5863
5378	UGUCCCCA A CCCACUCU	4578	AGAGTGGG GGCTAGCTACAACGA TGGGGACA	5864
5382	CCCAACCC A CUCUCACC	4579	GGTGAGAG GGCTAGCTACAACGA GGGTTGGG	5865
5388	CCACUCUC A CCCCGCAA	4580	TTGCGGGG GGCTAGCTACAACGA GAGAGTGG	5866
5393	CUCACCCC G CAACCCAU	4581	ATGGGTTG GGCTAGCTACAACGA GGGGTGAG	5867
5396	ACCCCGCA A CCCAUCAG	4582	CTGATGGG GGCTAGCTACAACGA TGCGGGGT	5868
5400	CGCAACCC A UCAGUAUU	4583	AATACTGA GGCTAGCTACAACGA GGGTTGCG	5869
5404	ACCCAUCA G UAUUUUAG	4584	CTAAAATA GGCTAGCTACAACGA TGATGGGT	5870
5406	CCAUCAGU A UUUUAGUU	4585	AACTAAAA GGCTAGCTACAACGA ACTGATGG	5871
5412	GUAUUUUA G UUAUUUGG	4586	CCAAATAA GGCTAGCTACAACGA TAAAATAC	5872
5415	UUUUAGUU A UUUGGCCU	4587	AGGCCAAA GGCTAGCTACAACGA AACTAAAA	5873
5420	GUUAUUUG G CCUCUACU	4588	AGTAGAGG GGCTAGCTACAACGA CAAATAAC	5874
5426	UGGCCUCU A CUCCAGUA	4589	TACTGGAG GGCTAGCTACAACGA AGAGGCCA	5875
5432	CUACUCCA G UAAACCUG	4590	CAGGTTTA GGCTAGCTACAACGA TGGAGTAG	5876
5436	UCCAGUAA A CCUGAUUG	4591	CAATCAGG GGCTAGCTACAACGA TTACTGGA	5877
5441	UAAACCUG A UUGGGUUU	4592	AAACCCAA GGCTAGCTACAACGA CAGGTTTA	5878
5446	CUGAUUGG G UUUGUUCA	4593	TGAACAAA GGCTAGCTACAACGA CCAATCAG	5879
5450	UUGGGUUU G UUCACUCU	4594	AGAGTGAA GGCTAGCTACAACGA AAACCCAA	5880
5454	GUUUGUUC A CUCUCUGA	4595	TCAGAGAG GGCTAGCTACAACGA GAACAAAC	5881
5463	CUCUCUGA A UGAUUAUU	4596	AATAATCA GGCTAGCTACAACGA TCAGAGAG	5882
5466	UCUGAAUG A UUAUUAGC	4597	GCTAATAA GGCTAGCTACAACGA CATTCAGA	5883
5469	GAAUGAUU A UUAGCCAG	4598	CTGGCTAA GGCTAGCTACAACGA AATCATTC	5884
5473	GAUUAUUA G CCAGACUU	4599	AAGTCTGG GGCTAGCTACAACGA TAATAATC	5885
5478	UUAGCCAG A CUUCAAAA	4600	TTTTGAAG GGCTAGCTACAACGA CTGGCTAA	5886
5486	ACUUCAAA A UUAUUUUA	4601	TAAAATAA GGCTAGCTACAACGA TTTGAAGT	5887
5489	UCAAAAUU A UUUUAUAG	4602	CTATAAAA GGCTAGCTACAACGA AATTTTGA	5888
5494	AUUAUUUU A UAGCCCAA	4603	TTGGGCTA GGCTAGCTACAACGA AAAATAAT	5889
5497	AUUUUAUA G CCCAAAUU	4604	AATTTGGG GGCTAGCTACAACGA TATAAAAT	5890
5503	UAGCCCAA A UUAUAACA	4605	TGTTATAA GGCTAGCTACAACGA TTGGGCTA	5891
5506	CCCAAAUU A UAACAUCU	4606	AGATGTTA GGCTAGCTACAACGA AATTTGGG	5892
5509	AAAUUAUA A CAUCUAUU	4607	AATAGATG GGCTAGCTACAACGA TATAATTT	5893
5511	AUUAUAAC A UCUAUUGU	4608	ACAATAGA GGCTAGCTACAACGA GTTATAAT	5894
5515	UAACAUCU A UUGUAUUA	4609	TAATACAA GGCTAGCTACAACGA AGATGTTA	5895
5518	CAUCUAUU G UAUUAUUU	4610	AAATAATA GGCTAGCTACAACGA AATAGATG	5896
5520	UCUAUUGU A UUAUUUAG	4611	CTAAATAA GGCTAGCTACAACGA ACAATAGA	5897
5523	AUUGUAUU A UUUAGACU	4612	AGTCTAAA GGCTAGCTACAACGA AATACAAT	5898
5529	UUAUUUAG A CUUUUAAC	4613	GTTAAAAG GGCTAGCTACAACGA CTAAATAA	5899
5536	GACUUUUA A CAUAUAGA	4614	TCTATATG GGCTAGCTACAACGA TAAAAGTC	5900
5538	CUUUUAAC A UAUAGAGC	4615	GCTCTATA GGCTAGCTACAACGA GTTAAAAG	5901
5540	UUUAACAU A UAGAGCUA	4616	TAGCTCTA GGCTAGCTACAACGA ATGTTAAA	5902
5545	CAUAUAGA G CUAUUUCU	4617	AGAAATAG GGCTAGCTACAACGA TCTATATG	5903
5548	AUAGAGCU A UUUCUACU	4618	AGTAGAAA GGCTAGCTACAACGA AGCTCTAT	5904
5554	CUAUUUCU A CUGAUUUU	4619	AAAATCAG GGCTAGCTACAACGA AGAAATAG	5905

5558	UUCUACUG A UUUUUGCC	4620	GGCAAAAA GGCTAGCTACAACGA CAGTAGAA	5906
5564	UGAUUUUU G CCCUUGUU	4621	AACAAGGG GGCTAGCTACAACGA AAAAATCA	5907
5570	UUGCCCUU G UUCUGUCC	4622	GGACAGAA GGCTAGCTACAACGA AAGGGCAA	5908
5575	CUUGUUCU G UCCUUUUU	4623	AAAAAGGA GGCTAGCTACAACGA AGAACAAG	5909
5597	AAAAGAAA A UGUGUUUU	4624	AAAACACA GGCTAGCTACAACGA TTTCTTTT	5910
5599	AAGAAAAU G UGUUUUUU	4625	AAAAAACA GGCTAGCTACAACGA ATTTTCTT	5911
5601	GAAAAUGU G UUUUUUGU	4626	ACAAAAAA GGCTAGCTACAACGA ACATTTTC	5912
5608	UGUUUUUU G UUUGGUAC	4627	GTACCAAA GGCTAGCTACAACGA AAAAAACA	5913
5613	UUUGUUUG G UACCAUAG	4628	CTATGGTA GGCTAGCTACAACGA CAAACAAA	5914
5615	UGUUUGGU A CCAUAGUG	4629	CACTATGG GGCTAGCTACAACGA ACCAAACA	5915
5618	UUGGUACC A UAGUGUGA	4630	TCACACTA GGCTAGCTACAACGA GGTACCAA	5916
5621	GUACCAUA G UGUGAAAU	4631	ATTTCACA GGCTAGCTACAACGA TATGGTAC	5917
5623	ACCAUAGU G UGAAAUGC	4632	GCATTTCA GGCTAGCTACAACGA ACTATGGT	5918
5628	AGUGUGAA A UGCUGGGA	4633	TCCCAGCA GGCTAGCTACAACGA TTCACACT	5919
5630	UGUGAAAU G CUGGGAAC	4634	GTTCCCAG GGCTAGCTACAACGA ATTTCACA	5920
5637	UGCUGGGA A CAAUGACU	4635	AGTCATTG GGCTAGCTACAACGA TCCCAGCA	5921
5640	UGGGAACA A UGACUAUA	4636	TATAGTCA GGCTAGCTACAACGA TGTTCCCA	5922
5643	GAACAAUG A CUAUAAGA	4637	TCTTATAG GGCTAGCTACAACGA CATTGTTC	5923
5646	CAAUGACU A UAAGACAU	4638	ATGTCTTA GGCTAGCTACAACGA AGTCATTG	5924
5651	ACUAUAAG A CAUGCUAU	4639	ATAGCATG GGCTAGCTACAACGA CTTATAGT	5925
5653	UAUAAGAC A UGCUAUGG	4640	CCATAGCA GGCTAGCTACAACGA GTCTTATA	5926
5655	UAAGACAU G CUAUGGCA	4641	TGCCATAG GGCTAGCTACAACGA ATGTCTTA	5927
5658	GACAUGCU A UGGCACAU	4642	ATGTGCCA GGCTAGCTACAACGA AGCATGTC	5928
5661	AUGCUAUG G CACAUAUA	4643	TATATGTG GGCTAGCTACAACGA CATAGCAT	5929
5663	GCUAUGGC A CAUAUAUU	4644	AATATATG GGCTAGCTACAACGA GCCATAGC	5930
5665	UAUGGCAC A UAUAUUUA	4645	TAAATATA GGCTAGCTACAACGA GTGCCATA	5931
5667	UGGCACAU A UAUUUAUA	4646	TATAAATA GGCTAGCTACAACGA ATGTGCCA	5932
5669	GCACAUAU A UUUAUAGU	4647	ACTATAAA GGCTAGCTACAACGA ATATGTGC	5933
5673	AUAUAUUU A UAGUCUGU	4648	ACAGACTA GGCTAGCTACAACGA AAATATAT	5934
5676	UAUUUAUA G UCUGUUUA	4649	TAAACAGA GGCTAGCTACAACGA TATAAATA	5935
5680	UAUAGUCU G UUUAUGUA	4650	TACATAAA GGCTAGCTACAACGA AGACTATA	5936
5684	GUCUGUUU A UGUAGAAA	4651	TTTCTACA GGCTAGCTACAACGA AAACAGAC	5937
5686	CUGUUUAU G UAGAAACA	4652	TGTTTCTA GGCTAGCTACAACGA ATAAACAG	5938
5692	AUGUAGAA A CAAAUGUA	4653	TACATTTG GGCTAGCTACAACGA TTCTACAT	5939
5696	AGAAACAA A UGUAAUAU	4654	ATATTACA GGCTAGCTACAACGA TTGTTTCT	5940
5698	AAACAAAU G UAAUAUAU	4655	ATATATTA GGCTAGCTACAACGA ATTTGTTT	5941
5701	CAAAUGUA A UAUAUUAA	4656	TTAATATA GGCTAGCTACAACGA TACATTTG	5942
5703	AAUGUAAU A UAUUAAAG	4657	CTTTAATA GGCTAGCTACAACGA ATTACATT	5943
5705	UGUAAUAU A UUAAAGCC	4658	GGCTTTAA GGCTAGCTACAACGA ATATTACA	5944
5711	AUAUUAAA G CCUUAUAU	4659	ATATAAGG GGCTAGCTACAACGA TTTAATAT	5945
5716	AAAGCCUU A UAUAUAAU	4660	ATTATATA GGCTAGCTACAACGA AAGGCTTT	5946
5718	AGCCUUAU A UAUAAUGA	4661	TCATTATA GGCTAGCTACAACGA ATAAGGCT	5947
5720	CCUUAUAU A UAAUGAAC	4662	GTTCATTA GGCTAGCTACAACGA ATATAAGG	5948
5723	UAUAUAUA A UGAACUUU	4663	AAAGTTCA GGCTAGCTACAACGA TATATATA	5949
5727	UAUAAUGA A CUUUGUAC	4664	GTACAAAG GGCTAGCTACAACGA TCATTATA	5950
5732	UGAACUUU G UACUAUUC	4665	GAATAGTA GGCTAGCTACAACGA AAAGTTCA	5951
5734	AACUUUGU A CUAUUCAC	4666	GTGAATAG GGCTAGCTACAACGA ACAAAGTT	5952
5737	UUUGUACU A UUCACAUU	4667	AATGTGAA GGCTAGCTACAACGA AGTACAAA	5953
5741	UACUAUUC A CAUUUUGU	4668	ACAAAATG GGCTAGCTACAACGA GAATAGTA	5954
5743	CUAUUCAC A UUUUGUAU	4669	ATACAAAA GGCTAGCTACAACGA GTGAATAG	5955
5748	CACAUUUU G UAUCAGUA	4670	TACTGATA GGCTAGCTACAACGA AAAATGTG	5956
5750	CAUUUUGU A UCAGUAUU	4671	AATACTGA GGCTAGCTACAACGA ACAAAATG	5957
5754	UUGUAUCA G UAUUAUGU	4672	ACATAATA GGCTAGCTACAACGA TGATACAA	5958

5756	GUAUCAGU A UUAUGUAG	4673	CTACATAA GGCTAGCTACAACGA ACTGATAC	5959
5759	UCAGUAUU A UGUAGCAU	4674	ATGCTACA GGCTAGCTACAACGA AATACTGA	5960
5761	AGUAUUAU G UAGCAUAA	4675	TTATGCTA GGCTAGCTACAACGA ATAATACT	5961
5764	AUUAUGUA G CAUAACAA	4676	TTGTTATG GGCTAGCTACAACGA TACATAAT	5962
5766	UAUGUAGC A UAACAAAG	4677	CTTTGTTA GGCTAGCTACAACGA GCTACATA	5963
5769	GUAGCAUA A CAAAGGUC	4678	GACCTTTG GGCTAGCTACAACGA TATGCTAC	5964
5775	UAACAAAG G UCAUAAUG	4679	CATTATGA GGCTAGCTACAACGA CTTTGTTA	5965
5778	CAAAGGUC A UAAUGCUU	4680	AAGCATTA GGCTAGCTACAACGA GACCTTTG	5966
5781	AGGUCAUA A UGCUUUCA	4681	TGAAAGCA GGCTAGCTACAACGA TATGACCT	5967
5783	GUCAUAAU G CUUUCAGC	4682	GCTGAAAG GGCTAGCTACAACGA ATTATGAC	5968
5790	UGCUUUCA G CAAUUGAU	4683	ATCAATTG GGCTAGCTACAACGA TGAAAGCA	5969
5793	UUUCAGCA A UUGAUGUC	4684	GACATCAA GGCTAGCTACAACGA TGCTGAAA	5970
5797	AGCAAUUG A UGUCAUUU	4685	AAATGACA GGCTAGCTACAACGA CAATTGCT	5971
5799	CAAUUGAU G UCAUUUUA	4686	TAAAATGA GGCTAGCTACAACGA ATCAATTG	5972
5802	UUGAUGUC A UUUUAUUA	4687	TAATAAAA GGCTAGCTACAACGA GACATCAA	5973
5807	GUCAUUUU A UUAAAGAA	4688	TTCTTTAA GGCTAGCTACAACGA AAAATGAC	5974
5815	AUUAAAGA A CAUUGAAA	4689	TTTCAATG GGCTAGCTACAACGA TCTTTAAT	5975
5817	UAAAGAAC A UUGAAAAA	4690	TTTTTCAA GGCTAGCTACAACGA GTTCTTTA	5976

Input Sequence = AF035121. Cut Site = R/Y
Arm Length = 8. Core Sequence = GGCTAGCTACAACGA
AF035121 (Homo sapiens KDR/flk-1 protein mRNA, complete cds.; Acc# AF035121; 5830 bp)

CLAIMS

1. A compound having Formula II: (SEQ ID NO: 5978)

5'-$u_sa_sc_s$ $a_s$au ucU GAu Gag gcg aaa gcc Gaa Aag aca aB-3'

wherein each **a** is 2'-O-methyl adenosine nucleotide, each **g** is a 2'-O-methyl guanosine nucleotide, each **c** is a 2'-O-methyl cytidine nucleotide, each **u** is a 2'-O-methyl uridine nucleotide, each **A** is adenosine, each **G** is guanosine, each **s** individually represents a phosphorothioate internucleotide linkage, **U** is 2'-deoxy-2'-C-allyl uridine, and **B** is an inverted deoxyabasic moiety.

2. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

3. A method of administering to a cell the compound of claim 1 comprising contacting said cell with the compound under conditions suitable for said administration.

4. The method of claim 3, wherein said cell is a mammalian cell.

5. The method of claim 3, wherein said cell is a human cell.

6. The method of claim 3, wherein said administration is in the presence of a delivery reagent.

7. The method of claim 6, wherein said delivery reagent is a lipid.

8. The method of claim 7, wherein said lipid is a cationic lipid.

9. The method of claim 7, wherein said lipid is a phospholipid.

10. The method of claim 6, wherein said delivery reagent is a liposome.

11. A method of administering to a cell the compound of claim 1 in conjunction with one or more other drug comprising contacting said cell

with the compound and the other drug(s) under conditions suitable for said administration.

12. A method of inhibiting ocular angiogenesis in a subject comprising the step of contacting said subject with the compound of claim 1 under conditions suitable for said inhibition.

13. The method of claim 12, wherein said angiogenesis is associated with diabetic retinopathy.

14. The method of claim 12, wherein said angiogenesis is associated with age related diabetic retinopathy.

15. A method of cleaving RNA comprising a sequence of KDR RNA comprising contacting the compound of claim 1 with said RNA under conditions suitable for the cleavage of said RNA.

16. The method of claim 15, wherein said cleavage is carried out in the presence of a divalent cation.

17. The method of claim 16, wherein said divalent cation is Mg2+.

18. A method of administering to a mammal the compound of claim 1 comprising contacting said mammal with the compound under conditions suitable for said administration.

19. The method of claim 18, wherein said mammal is a human.

20. The method of claim 18 wherein said administration is in the presence of a delivery reagent.

21. The method of claim 18, wherein said delivery reagent is a lipid.

22. The method of claim 21, wherein said lipid is a cationic lipid.

23. The method of claim 21, wherein said lipid is a phospholipid.

24. The method of claim 20, wherein said delivery reagent is a liposome.

25. A method for treating a subject having endometriosis, comprising contacting said subject with a nucleic acid molecule that modulates the expression of VEGF, VEGFR1, and/or VEGFR2, under conditions suitable for said treatment.

26. The method of claim 25, wherein said nucleic acid molecule is an enzymatic nucleic acid molecule.

27. The method of claim 25, wherein said nucleic acid molecule is an antisense nucleic acid molecule.

28. The method of claim 25, wherein said nucleic acid molecule is a dsRNA nucleic acid molecule.

29. The method of claim 25, wherein said nucleic acid molecule is a nucleic acid aptamer.

30. The method of claim 25, wherein said nucleic acid molecule comprises a sequence having SEQ ID NO: 5977.

31. The method of claim 26, wherein said enzymatic nucleic acid molecule has an endonuclease activity to cleave RNA encoded by an VEGFR1 and/or VEGFR2 gene.

32. The method of claim 26, wherein said enzymatic nucleic acid molecule is in a hammerhead configuration.

33. The method of claim 26, wherein said enzymatic nucleic acid molecule is in an Inozyme configuration.

34. The method of claim 26, wherein said enzymatic nucleic acid molecule is in a Zinzyme configuration.

35. The method of claim 26, wherein said enzymatic nucleic acid molecule is in a DNAzyme configuration.

36. The method of claim 26, wherein said enzymatic nucleic acid molecule is in a G-cleaver configuration.

37. The method of claim 26, wherein said enzymatic nucleic acid molecule is in an Amberzyme configuration.

38. The method of claim 26, wherein said enzymatic nucleic acid molecule is an allozyme.

39. The method of claim 25, wherein said nucleic acid molecule is chemically synthesized.

40. The method of claim 25, wherein said nucleic acid molecule comprises at least one 2'-sugar modification.

41. The method of claim 25, wherein said nucleic acid molecule comprises at least one nucleic acid base modification.

42. The method of claim 25, wherein said nucleic acid molecule comprises at least one phosphate backbone modification.

43. The method of claim 25, wherein said subject is a human.

44. A method for treating a subject having endometriosis, comprising administering to the subject a nucleic acid molecule that modulates the expression of VEGF, VEGFR1, and/or VEGFR2, under conditions suitable for said treatment.

45. The method of claim 44 wherein said administration is in the presence of a delivery reagent.

46. The method of claim 45, wherein said delivery reagent is a lipid.

47. The method of claim 46, wherein said lipid is a cationic lipid.

48. The method of claim 46, wherein said lipid is a phospholipid.

49. The method of claim 45, wherein said delivery reagent is a liposome.

50. The method of claim 44, further comprising administering one or more other drug(s).

51. The method of claim 50, wherein said other drug(s) are chosen from GnRH (gonadotropin releasing hormone) agonists, Lupron Depot (Leuprolide Acetate), Synarel (naferalin acetate), Zolodex (goserelin acetate), Suprefact (buserelin acetate), Danazol, and oral contraceptives.

52. A compound having Formula I: (SEQ ID NO: 5977)

5' $g_sa_sg_su_s$ugc<u>U</u>GAuGagg ccgaaa ggccGaaAgucugB 3'

wherein each **a** is 2'-O-methyl adenosine nucleotide, each **g** is a 2'-O-methyl guanosine nucleotide, each **c** is a 2'-O-methyl cytidine nucleotide, each **u** is a 2'-O-methyl uridine nucleotide, each **A** is adenosine, each **G** is guanosine, each s individually represents a phosphorothioate internucleotide linkage, **<u>U</u>** is 2'-deoxy-2'-C-allyl uridine, and **B** is an inverted deoxyabasic moiety.

53. A composition comprising a compound of claim 52 in a pharmaceutically acceptable carrier or diluent.

54. A method of administering to a cell the compound of claim 52 comprising contacting said cell with the compound under conditions suitable for said administration.

55. The method of claim 54, wherein said cell is a mammalian cell.

56. The method of claim 54, wherein said cell is a human cell.

57. The method of claim 54, wherein said administration is in the presence of a delivery reagent.

58. The method of claim 57, wherein said delivery reagent is a lipid.

59. The method of claim 58, wherein said lipid is a cationic lipid.

60. The method of claim 58, wherein said lipid is a phospholipid.

61. The method of claim 57, wherein said delivery reagent is a liposome.

62. A method of administering to a cell the compound of claim 52 in conjunction with a chemotherapeutic agent comprising contacting said cell with the compound and the chemotherapeutic agent under conditions suitable for said administration.

63. The method of claim 62, wherein said chemotherapeutic agent is 5-fluoro uridine.

64. The method of claim 62, wherein said chemotherapeutic agent is Leucovorin.

65. The method of claim 62, wherein said chemotherapeutic agent is chosen from Irinotecan, CAMPTOSAR®, CPT-11, Camptothecin-11, or Campto.

66. The method of claim 62, wherein said chemotherapeutic agent is Paclitaxel.

67. The method of claim 62, wherein said chemotherapeutic agent is Carboplatin.

68. A mammalian cell comprising the compound of claim 52..

69. The mammalian cell of claim 68, wherein said mammalian cell is a human cell.

70. A method of inhibiting angiogenesis in a subject, comprising the step of contacting said subject with the compound of claim 52, under conditions suitable for said inhibition.

71. The method of claim 70, wherein said angiogenesis is tumor angiogenesis.

72. A method of treatment of a subject having a condition associated with an increased level of VEGF receptor comprising contacting cells of said subject with the compound of claim 52, under conditions suitable for said treatment.

73. The method of claim 72 further comprising the use of one or more drug therapies under conditions suitable for said treatment.

74. A method of cleaving RNA comprising a sequence of VEGFR1 (flt-1), comprising contacting the compound of claim 52 with said RNA under conditions suitable for the cleavage of said RNA.

75. The method of claim 74, wherein said cleavage is carried out in the presence of a divalent cation.

76. The method of claim 75, wherein said divalent cation is Mg2+.

77. The method of claim 72, wherein said condition is cancer.

78. The method of claim 77, wherein said cancer is breast cancer.

79. The method of claim 77, wherein said cancer is lung cancer.

80. The method of claim 77, wherein said cancer is colorectal cancer.

81. The method of claim 77, wherein said cancer is renal cancer.

82. The method of claim 77, wherein said cancer is melanoma.

83. The method of claim 77, wherein said cancer is pancreatic cancer.

84. The method of claim 79, wherein said lung cancer is non-small cell lung carcinoma.

85. The method of claim 81, wherein said renal cancer is renal cell carcinoma.

86. The method of claim 73, wherein said other therapy is 5-fluoro uridine.

87. The method of claim 73, wherein said other therapy is Leucovorin.

88. The method of claim 73, wherein said other therapy is Irinotecan, CAMPTOSAR®, CPT-11, Camptothecin-11, or Campto.

89. The method of claim 73, wherein said other therapy is Paclitaxel.

90. The method of claim 73, wherein said other therapy is Carboplatin.

91. A method of administering to a mammal the compound of claim 52 comprising contacting said mammal with the compound under conditions suitable for said administration.

92. The method of claim 91, wherein said mammal is a human.

93. The method of claim 91, wherein said administration is in the presence of a delivery reagent.

94. The method of claim 93, wherein said delivery reagent is a lipid.

95. The method of claim 94, wherein said lipid is a cationic lipid.

96. The method of claim 94, wherein said lipid is a phospholipid.

97. The method of claim 93, wherein said delivery reagent is a liposome.

98. A method of administering to a mammal the compound of claim 52 in conjunction with a chemotherapeutic agent comprising contacting said mammal with the compound and the chemotherapeutic agent under conditions suitable for said administration.

99. The method of claim 98, wherein said chemotherapeutic agent is 5-fluoro uridine.

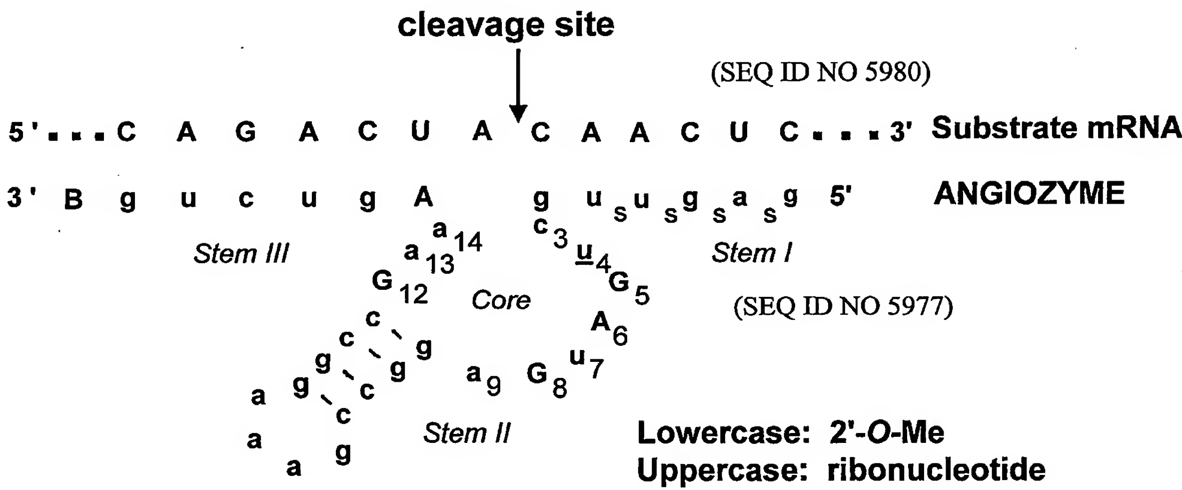
100. The method of claim 98, wherein said chemotherapeutic agent is Leucovorin.

101. The method of claim 98, wherein said chemotherapeutic agent is Irinotecan, CAMPTOSAR®, CPT-11, Camptothecin-11, or Campto.

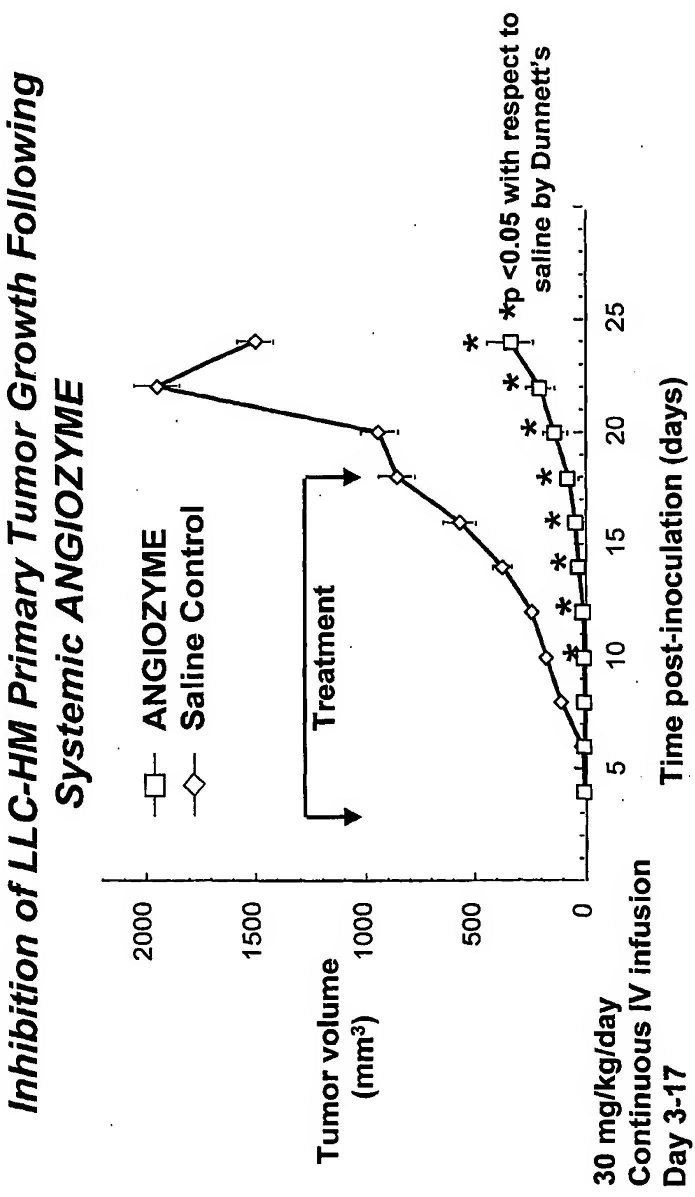
102. The method of claim 98, wherein said chemotherapeutic agent is Paclitaxel.

103. The method of claim 98, wherein said chemotherapeutic agent is Carboplatin.

Figure 1: Anti-Flt-1 Ribozyme: ANGIOZYME



Lowercase: 2'-*O*-Me
Uppercase: ribonucleotide
B: inverted deoxy abasic
s: phosphorothioate
$\underline{u}_4$: 2'- *C*-allyl



Inhibition of LLC-HM Primary Tumor Growth Following Systemic ANGIOZYME
ANGIOZYME
Saline Control
Treatment
Tumor volume (mm3)
2000
1500
1000
500
0
5
10
15
20
25
Time post-inoculation (days)
*p <0.05 with respect to saline by Dunnett's
30 mg/kg/day
Continuous IV infusion
Day 3-17

Figure 2

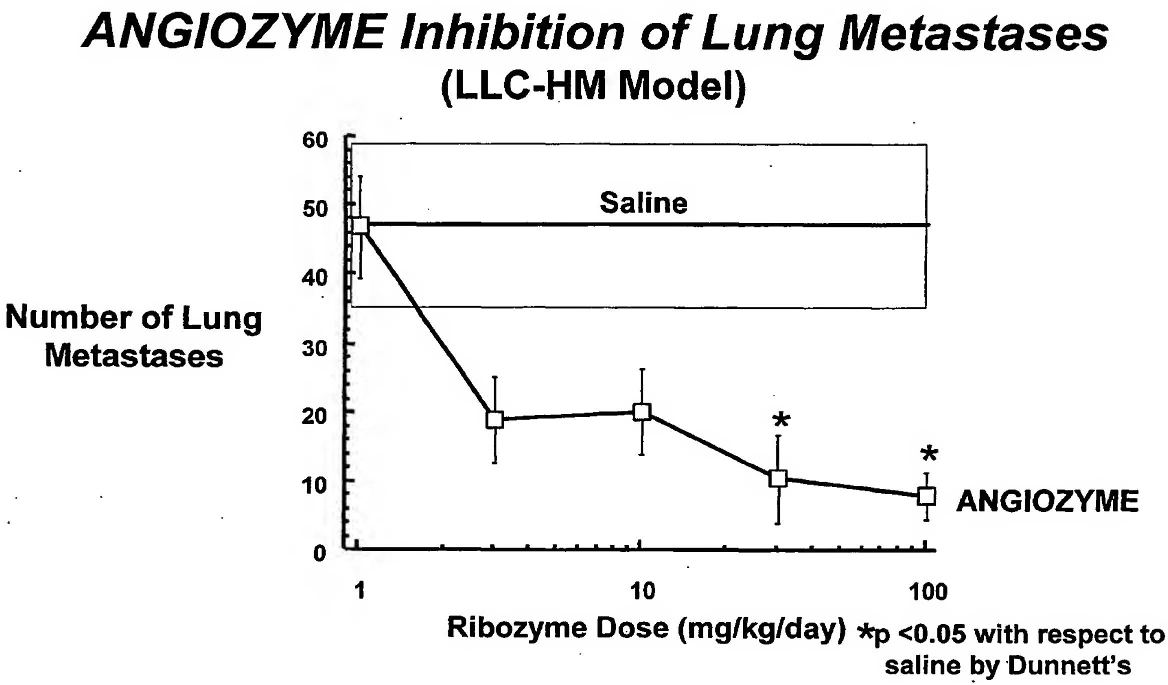
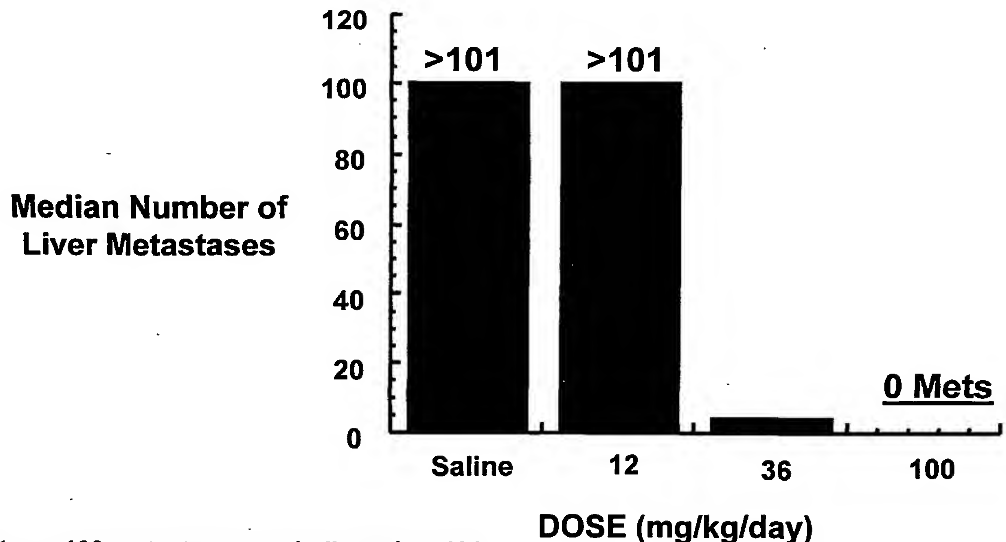

ANGIOZYME Inhibition of Lung Metastases
(LLC-HM Model)
Number of Lung Metastases
60
50
40
30
20
10
0
Saline
*
*
ANGIOZYME
1
10
100
Ribozyme Dose (mg/kg/day)
*p <0.05 with respect to saline by Dunnett's

Figure 3

Effect of ANGIOZYME on Liver Metastases in a Colorectal Cancer Model



Note: > 100 metastases are indicated as 101.

Figure 4

Figure 5: **Plasma concentration profile of ANGIOZYME after a single subcutaneous dose of 10, 30, 100 or 300 mg/m^2**

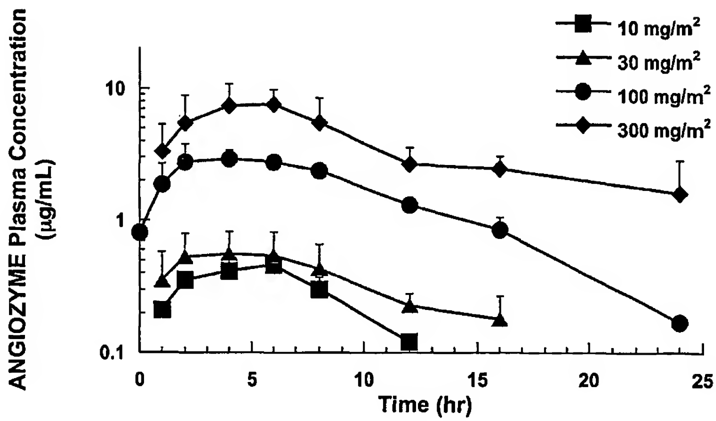


Figure 6: Examples of Nuclease Stable Ribozyme Motifs

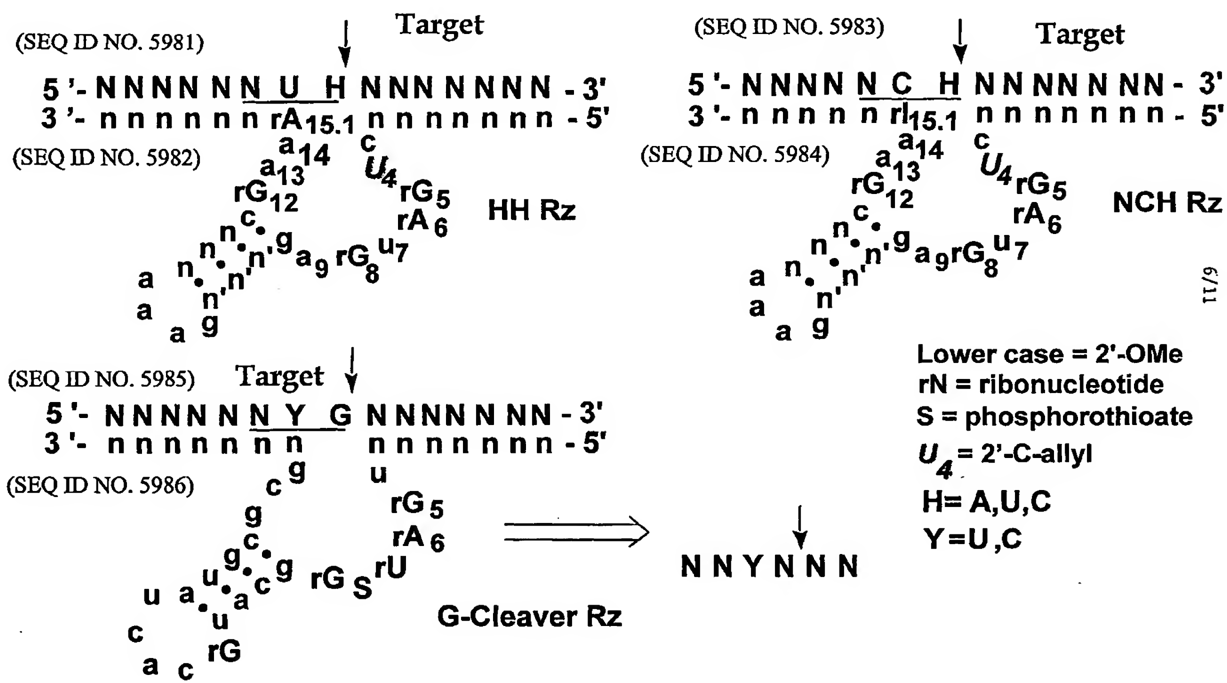
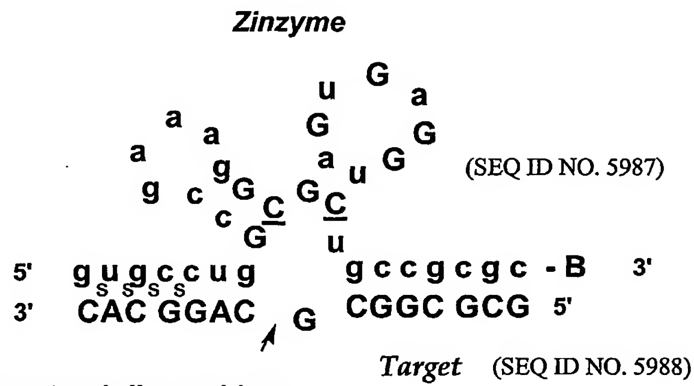


Figure 7: Stabilized Zinzyme Ribozyme Motif



Legend

Uppercase: indicates natural ribo residues

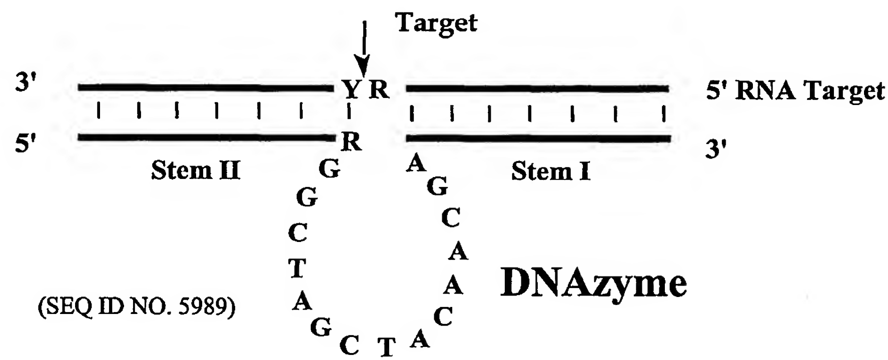
C : indicates 2'-deoxy-2'-amino Cytidine

Lowercase: 2'-O-methyl

S: phosphorothioate/phosphorodithioate linkage

B: 3'-3' abasic moiety

Figure 8: DNAzyme Motif



Legend

Y = U or C
R = A or G

Figure 9: Soluble VEGFR1 Reduction

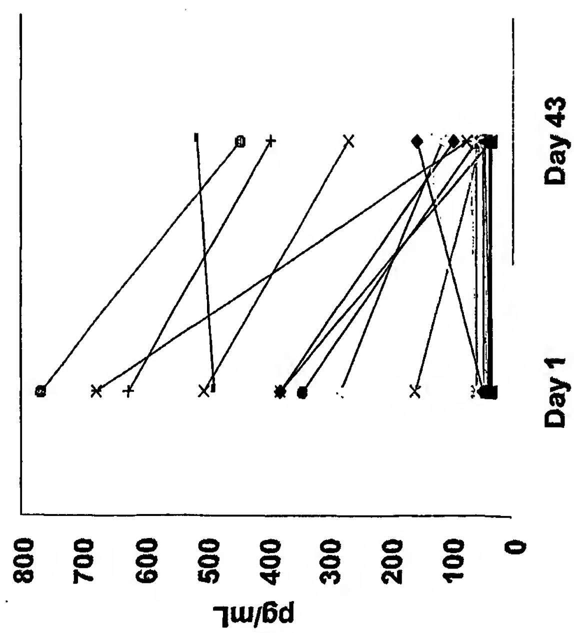
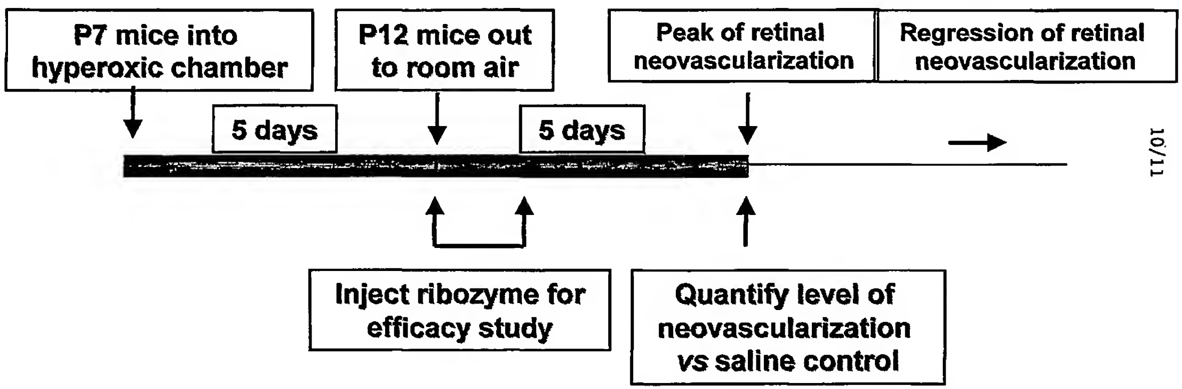
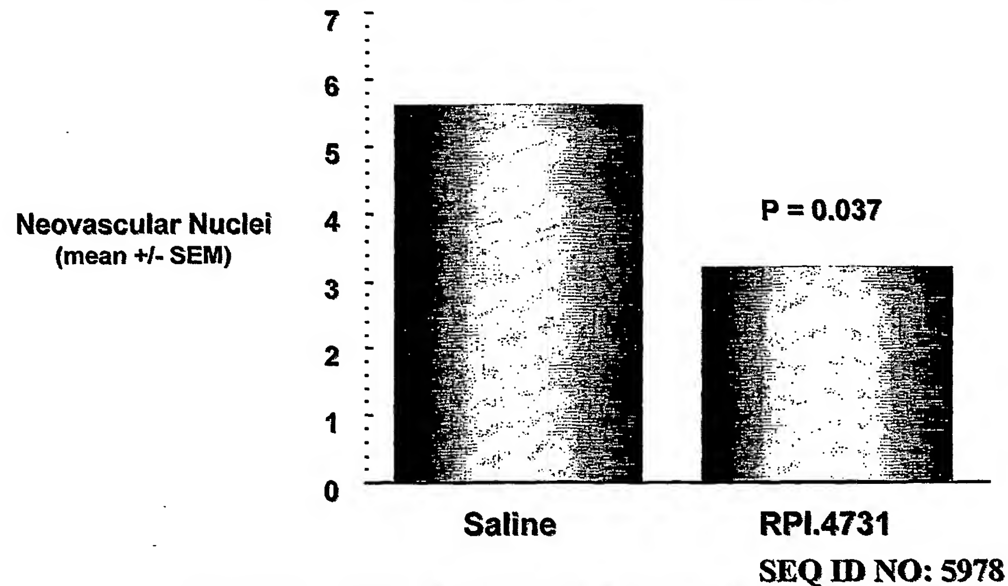


Figure 10: Mouse Model of Proliferative Retinopathy



Note: Peak VEGF levels noted 12 hr after exposure to room air

Figure 11: RPI.4731 Reduces Hypoxia-Induced Retinal Neovascularization in Neonatal Mice



Results: ~40% decrease in retinal neovascularization following two intraocular injections of RPI.4731

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